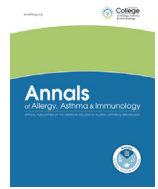




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The Asthma Controller Step-down Yardstick

Bradley E. Chipps, MD^{*}; Leonard B. Bacharier, MD[†]; Kevin R. Murphy, MD[‡];
David Lang, MD[§]; Judith R. Farrar, PhD[¶]; Matthew Rank, MD[#];
John Oppenheimer, MD^{**}; Robert S. Zeiger, MD, PhD^{††}

^{*} Capital Allergy & Respiratory Disease Center, Sacramento, California

[†] Washington University School of Medicine and St. Louis Children's Hospital, Division of Allergy, Immunology and Pulmonary Medicine, Saint Louis, Missouri

[‡] Boys Town National Research Hospital, Boys Town, Nebraska

[§] Division of Allergy and Clinical Immunology, Cleveland Clinic Foundation, Cleveland, Ohio

[¶] Academic Services Connection, Inc., Pittsford, New York

[#] Division of Allergy, Asthma, and Clinical Immunology, Mayo Clinic, Scottsdale, Arizona

^{**} Rutgers Medical School, Newark, New Jersey

^{††} Kaiser Permanente Southern California Region, Department of Allergy and Research and Evaluation, San Diego and Pasadena, California

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ABSTRACT

Asthma guidelines recommend a control-based approach to disease management in which the assessment of impairment and risk is linked to step-based therapy. Using this model, controller treatment is adjusted—upward or downward—according to a patient's level of asthma control over time. Strategies for stepping up controller therapy are well described, and the adult and pediatric Asthma Yardsticks provide operational recommendations based on patient profiles. Strategies for stepping down controller treatment are less clear, although stepping down to the minimum effective therapy is important and should be considered when a patient's asthma has been well controlled for an adequate period as defined by risk and impairment. This Yardstick presents recommendations for when and how to step down asthma controller therapy according to guideline-defined control levels. The objective is to provide clinicians who treat patients with asthma with a practical and clinically relevant framework for implementing a step-down in controller therapy.

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Introduction

Guidelines for asthma recommend a series of treatment steps (Fig 1) as a framework for disease management.^{1,2} The steps allow individualized adjustments in controller therapy in an upward or downward manner in response to a patient's level of asthma control over time. For patients with inadequately controlled asthma, a

step-up is recommended.^{1,2} Strategies for stepping up controller therapy are described in detail in the adult and pediatric Asthma Yardsticks.^{3,4} For patients whose asthma has been well controlled for at least 3 months (or longer for the highest risk patients), controller treatment may be stepped down. Comprehensive reviews are available that discuss the challenges of reducing therapy and potential strategies for a step-down.^{5–7} However, supporting

Reprints: Bradley E. Chipps, MD, FAAP, FAAAAI, FCCP, Medical Director, Capital Allergy & Respiratory Disease Center, Sacramento, CA 95819; E-mail: bchipps@capitalallergy.com.

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data are limited; and neither how to identify patients appropriate for step-down nor the operational aspects of stepping down therapy are clearly defined.⁸ This Yardstick presents recommendations for stepping down asthma controller therapy according to guideline-defined control levels (Fig 1), based on the available data and the authors' clinical experience.

Stepping down controller therapy serves to¹:

- Identify the minimum effective treatment that will maintain well-controlled asthma based on both impairment and risk domains
- Minimize the risk of adverse effects from higher doses of medication(s) than may be needed to maintain control

Additionally, stepping down therapy can simplify the patient's treatment regimen and may enhance adherence, because reducing exposure to higher doses of medication(s) is generally consistent with patient values and preferences.^{9,10} A step-down also has the potential to reduce treatment costs.^{1,11} Tapering treatment also may be used to re-assess a current diagnosis of asthma.^{12,13} Considerations for stepping down asthma therapy and reasons for not stepping down therapy are shown in Table 1.

When and how to implement a step-down in therapy is not always clear, and the timing and process may vary between patients. Factors to consider before attempting to step down controller therapy include: 1) the patient's current and previous levels of asthma control, especially the frequency and severity of previous asthma exacerbations; 2) the patient's current and previous patterns of asthma control (eg, seasonal variation); 3) the time lapsed since the patient's last asthma exacerbation; 4) factors contributing to symptom instability; and 5) potential barriers to success (Table 2).⁸

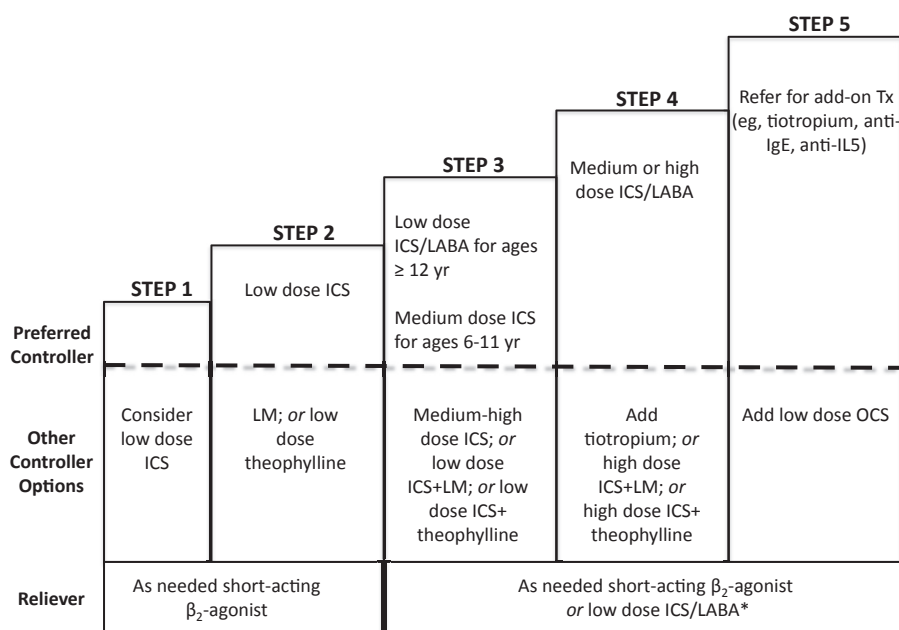
Asthma control is defined according to the frequency and intensity of symptoms, functional limitations, and potential negative effects of treatment (eTable 1).^{1–4} Current guidance suggests that a reduction in controller therapy may be considered when disease control has been maintained for several months (eg, 3–6 months),

depending on the patient's initial level of severity.¹ For patients with more severe asthma, a longer period of symptom stability may be needed.^{14,15}

Any step-down of asthma treatment should be considered as a therapeutic trial, with the outcome evaluated according to symptom control, lung function, and exacerbation frequency. Exacerbations are a particularly significant measure and may increase if treatment is stepped down too quickly or too far, even if symptoms appear to be reasonably controlled.^{1,8} Validated tools for assessing control and treatment response are available (eTable 2), and they can be used to determine when to consider a step-down in therapy and to monitor the result of treatment reduction. Monitoring is critical. Before stepping down treatment, the patient should be provided with a written asthma action plan that describes the step-down protocol, how to self-monitor asthma control, instructions for what to do if symptoms worsen, and when to call the doctor.¹

Factors that could negatively impact step-down therapy (Table 2) also should be evaluated before proceeding. These can increase the risk of symptom instability, and patients may require extra care if treatment is tapered. A careful medical history is critical. The impact of poor adherence with therapy, poor device technique, lack of understanding of asthma and its treatment, perceptions of step-care, and lack of access to care is more difficult to decipher, but they are all elements that can impede a successful step-down.⁶ Finally, treatment reduction should not occur during times of potential symptom liability for the patient, such as during pregnancy, illness, peak virus or allergen seasons, or a period of travel or high stress (eg, related to work or family concerns).

Once a step-down is determined to be appropriate, the approach should be individualized according to the patient's current treatment, risk factors, values, and preferences. Step-down strategies by guideline level of severity are described in the following pages. The supporting evidence is limited in terms of both medication choices and the operational aspects of stepping down. Considerations for children are included in each section as appropriate. Development of this Yardstick is described in the [Supplementary Materials \(eMethods\)](#).



*For patients prescribed beclomethasone/formoterol or budesonide/formoterol

Figure 1. Step care therapy according to GINA 2018.¹ Abbreviations: ICS, inhaled corticosteroid; IgE, immunoglobulin E; IL-5, interleukin-5; LABA, long-acting beta-agonist; LM, leukotriene modifier; OCS, oral corticosteroid; Tx, treatment(s).

Table 1
Reasons to Step Down or Not to Step Down Asthma Therapy^{5,6}

Consider stepping down treatment to:
• Re-assess a current diagnosis of asthma
• Decrease the potential adverse effects of asthma medications
• Address patient and family preferences about taking medications
• Reduce the burden of treatment (eg, time to take medications, remembering to take medications, having to take medications at work or school)
• Reduce the costs of treatment
• Simplify therapy and enhance adherence with treatment
Consider not stepping down treatment when:
• Reducing asthma medication may lead to an increased risk of having an asthma exacerbation or loss of control
• Whether the patient is using his/her asthma medications as indicated (eg, whether the patient has already self-reduced treatment) is unclear
• A seasonal maintenance of therapy is needed (eg, during the patient's allergy season or viral season)

Stepping Down from Step 2 Therapy

Stepping down from step 2 therapy is one of the most common step-down events for asthma patients because the step-down is often initiated by the patient through lapses in adherence, intentional or non-intentional, when symptoms are perceived to be controlled. A step-down at this level also may be used as a check on the diagnosis of asthma. Asthma is a dynamic condition, and remission is possible. Overdiagnosis and misdiagnosis also have been documented, likely related to a failure to confirm variable airflow limitation at the time of evaluation or to not recognizing conditions that mimic asthma symptoms (eg, vocal cord dysfunction, eosinophilic bronchitis, gastroesophageal reflux).^{12,13,16–18} Community studies have estimated that 30% to 35% of adults and children with physician-diagnosed asthma do not have the disease.^{12,13,16}

At step 2, most patients have been prescribed low-dose inhaled corticosteroid (ICS), and several step-down approaches may be considered: 1) continued daily use of a minimum dose of ICS,¹ 2) switching within step 2 to a leukotriene modifier (LM), particularly for patients who prefer an oral medication or who have difficulty using an inhaler,^{1,19} 3) switching to once-daily low-dose ICS/long-acting beta-agonist (LABA) combination,¹⁹ 4) using reliever medication (a short-acting β_2 -agonist, SABA) with or without ICS on an as-needed basis for intermittent symptoms,^{1,20–22} and 5) as-needed use of budesonide/formoterol.^{23–26}

Diagnostic Step-Down

To confirm the diagnosis (or exclusion) of asthma in the appropriate patient, gradual medication tapering is recommended over a series of physician visits that include monitoring the patient's symptoms and lung function testing. Fractional exhaled nitric oxide (FeNO), if measured, provides another option for monitoring a diagnostic step-down.^{12,13} Patients who have no evidence of worsening symptoms, increasing airflow obstruction, or increased FeNO after being weaned off all asthma medications may not have asthma, but continued monitoring after discontinuation is important because it may take a while before symptoms recur. If the diagnosis of asthma is confirmed, the patient then can be maintained on the minimal effective dose titrated.

Stepping Down When Asthma Is Confirmed

For patients already on relatively low doses of ICS, stepping down to an LM or to once-daily ICS/LABA are pathways to further reduce the daily dose of ICS. In a study by the American Lung Association Asthma Clinical Research Centers, 500 patients with asthma that was well controlled by twice-daily fluticasone propionate (FP, 100 μ g twice daily) were randomized to either continue

Table 2
Potential Barriers to Successfully Stepping Down Therapy^{1,6}

• Previous hospitalization/intensive care/intubation for asthma
• Frequent urgent care visits/ED visits for asthma
• Frequent oral corticosteroids for exacerbations
• Poor perception of symptoms
• Seasonal/environmental/situational triggers (eg, allergens, irritants, viruses, stress)
• Comorbid conditions contributing to morbidity (eg, rhinosinusitis, obesity, respiratory infection, gastroesophageal reflux disease, food allergy, psychiatric diagnoses)
• Difficulty using inhalers; improper technique
• Resistance to change; fear of using less medicine
• Prior lack of adherence to the management plan, which may reflect ○ Poor understanding of treatment ■ Belief that the medication does not help (eg, in relation to patients reporting that they cannot feel an immediate effect) ■ Belief that even controller medication can be taken intermittently (eg, when symptoms become “noticeable”) ○ Inconvenience, including using multiple medications/inhalers and having to take medications several times a day ○ Dislike of provider; distrust of medical establishments ○ Not recognizing symptoms or ignoring the need for using medication ○ Lack of parental support in following treatment plan ○ Family stress, emotional upsets; violence
• Nonwhite ethnicity
• Poverty ○ Lack of insurance or medication change not covered by insurance ○ Lack of access to health care
• Clinician perception of treatment (eg, lack of awareness of skewing risk/benefit analysis to ensure benefit)

twice-daily FP or to receive montelukast (5 or 10 mg at night) or FP/salmeterol (100 μ g/50 μ g) at night for 16 weeks.¹⁹ Asthma control, measured as the percentage of days on which patients were free of asthma symptoms, was similar across the 3 groups, but treatment failures were increased with randomization to montelukast (30.3%) compared with either FP group (20%, $P = .03$). Once-daily FP/salmeterol provided comparable clinical benefits to FP monotherapy, but at half the ICS dose.¹⁹

A complicating factor when making treatment decisions at this level is that patients with mild persistent asthma and infrequent symptoms may not see the value in taking a daily maintenance medication—even once daily.²³ They may prefer and may have stepped-down themselves to using a SABA only, for quick relief when needed. However, using a SABA without an inflammatory medication is associated with greater impairment, particularly during times of increased symptoms when overuse is likely.^{23,27,28} For these patients, consideration may be given to prescribing anti-inflammatory-reliever therapy on an as-needed basis, which has been shown to be effective with beclomethasone and SABAs^{20,21} and with as-needed use of budesonide/formoterol.^{22–26}

The two Symbicort Given as Needed in Mild Asthma (SYGMA) studies compared treatment with budesonide/formoterol with as-needed terbutaline and maintenance therapy with budesonide over a period of 52 weeks.^{23,24} The subjects were patients (≥ 12 years old) who had mild asthma that was either uncontrolled while using as-needed SABA reliever only or was well controlled while using maintenance therapy—either low-dose ICS or an LM (plus as-needed SABA).

In the SYGMA-1 trial, 3849 subjects were randomly assigned to twice-daily placebo plus as-needed terbutaline (0.5 mg), twice-daily placebo plus as-needed budesonide/formoterol (200 μ g/6 μ g), or twice-daily budesonide (200 μ g) maintenance therapy plus as-needed terbutaline (0.5 mg).²⁴ As-needed budesonide/formoterol was superior to as-needed terbutaline for the percentage of weeks with well-controlled asthma per patient, the primary outcome (34.4% vs 31.1% of weeks; odds ratio [OR], 1.14; 95% confidence interval [CI], 1.00–1.30; $P = .046$), but was inferior to budesonide maintenance therapy (34.4% vs 44.4%; OR, 0.64; 95% CI, 0.57–0.73). However, as-needed

budesonide/formoterol was non-inferior to budesonide maintenance therapy for reducing asthma exacerbations and resulted in a 64% lower rate of severe exacerbations than terbutaline alone (annualized exacerbation rate, 0.07 vs 0.20) and a 60% lower rate of moderate-to-severe exacerbations (annualized exacerbation rate, 0.14 vs 0.36). The median daily dose of ICS in the budesonide/formoterol group was 17% of that in the budesonide group (57 μ g and 340 μ g, respectively).²⁴

The SYGMA-2 trial included 4215 subjects who were randomized to 2 treatment groups: twice-daily placebo plus as-needed budesonide/formoterol (200 μ g/6 μ g) or twice-daily budesonide (200 μ g) maintenance therapy plus as-needed terbutaline (0.5 mg).²³ Again, budesonide/formoterol was non-inferior to budesonide alone for reducing exacerbations, but budesonide maintenance therapy was better for symptom control. The median daily dose of ICS in the budesonide/formoterol group was 25% of that in the budesonide maintenance group (66 μ g and 267 μ g, respectively).²³ A post-hoc analysis of 6 double-blind studies showed that the trends for adolescents ($n = 1847$) were similar to those for adults.²⁶ Data in children are needed.

Summary and Recommendations

Although symptoms may not be chronically bothersome for patients with milder asthma, airway inflammation and the risk of exacerbations are of concern. A systematic review and meta-analysis of 7 studies (1040 patients) reported a relative risk of 2.35 (1.88–2.92) for asthma exacerbations in patients who stopped ICS compared with those who continued using ICS.²⁹ Nonetheless, although guidelines recommend using low-dose ICS as maintenance therapy for patients with mild persistent asthma, adherence with regular treatment is lower in patients with infrequent symptoms. Patients with mild disease also may balk at using a daily corticosteroid for extended periods. A conversation with the patient about their current use of anti-inflammatory therapy is important; the patient should be encouraged to share his or her values and preferences and to participate in the clinical decision process. Educating the patient on the importance of using an anti-inflammatory therapy even when symptoms are infrequent is necessary. Additionally, an accurate assessment of whether the patient is likely to be adherent with a recommended treatment is important.

When stepping down from step 2 therapy, the authors recommend the following:

- For patients likely to be adherent with daily inhalational treatment, once-daily low-dose ICS monotherapy or once-daily low-dose ICS/LABA is recommended.
- For patients who are not likely to be adherent with, or prefer an alternative to, daily treatment, anti-inflammatory/reliever therapy should be used with a combination ICS and fast-acting SABA or LABA (formoterol).
- For patients who prefer oral therapy or who have difficulty using an inhaler, an LM can be used daily, plus an as-needed SABA as reliever medication.
- Based on the data and their combined clinical experience, the authors do not recommend that patients with mild persistent asthma, even those with infrequent symptoms, use as-needed SABA alone.

Stepping Down from Step 3 Therapy

Step 3 patients will be using 1 of 3 types of controller regimens: low-dose ICS/LABA, medium-dose ICS, or low-dose ICS + another medication (eg, LM).^{1,3,4} Patients with aspirin-exacerbated respiratory disease may be using zileuton.³⁰ A low-dose ICS/LABA strategy is preferred for most adult and adolescent patients, because patients can be maintained at lower doses of ICS compared with the other options.^{1,3,4} For school-age children (6–11 years old),

the guideline-recommended option is moderate-dose ICS.^{1,4} However, for adolescents and school-age children, heterogeneity in response has been demonstrated, and some of these patients may do better with options other than the guideline recommendation: ICS monotherapy, ICS/LABA, or ICS + LM.^{1,2,4,31,32} In a crossover comparison of these 3 strategies in children (6–17 years old) inadequately controlled with low-dose ICS monotherapy, the best response for most of the subjects was with ICS/LABA, which also permitted a greater than 50% reduction in the ICS dose compared with monotherapy.³¹

Before considering a step-down in therapy, the patient should be assessed for adequate asthma control and factors that may diminish success (Table 2), including adherence with the treatment plan, adequacy of inhalation technique, and previous allergic and seasonal trigger patterns. Reviewing the medical history for previous increases in controller therapy and corresponding responses as well as exacerbations in the previous year is essential.

As a frame of reference, the goal for a complete step-down from step 3 is to achieve the preferred controller therapy for step 2, namely, low-dose ICS monotherapy^{1–4} (Fig 1). A number of strategies may be considered, but all lack robust clinical trial evidence.

Patients Using Low-Dose ICS/LABA

The step-down choices for patients at step 3 whose symptoms have been controlled on low-dose ICS/LABA are 1) switching to an ICS/LABA combination at a lower dose of ICS; or 2) discontinuing the LABA while maintaining ICS monotherapy. Alternately, patients could be stepped down first to an ICS/LABA combination with a lower dose of ICS, and subsequently to ICS monotherapy.

In the past, the Food and Drug Administration (FDA) has supported the strategy of LABA discontinuation based on concerns about potential adverse effects of LABA.³³ Whether regular treatment with a LABA, even in combination with ICS, could predispose patients to untoward outcomes, including asthma-related morbidity and mortality, was an area of controversy. The outcomes of several recent large clinical trials and systematic reviews demonstrated that the risk of serious asthma-related adverse events with ICS/LABA was comparable to that for ICS monotherapy,^{34–40} and as a result in December 2017 the FDA removed the boxed warning about asthma-related death from the drug labels of medicines containing the combination.^{40–43}

The most recent Global Initiative for Asthma (GINA) document supports the first strategy—maintaining the patient on an ICS/LABA combination with a lower dose of ICS—with the rationale that continuing the LABA provides better symptom control than ICS alone.^{1,44} Based on the available data and their clinical experience, the authors favor tapering the dose of ICS/LABA either by using a lower-dose ICS in combination or switching to once-daily dosing of the combination product. Drawbacks exist. Using a lower-dose ICS in combination is limited by the available products (Table 3)—the patient may already be on the lowest dose of ICS; and switching to from twice-daily to once-daily dosing has not been approved by the FDA.

Few data are available to help decision-making for any of these strategies. The published literature contains a number of studies comparing step-down strategies for ICS/LABA combinations (Table 4), but most involve patients whose conditions are controlled on medium or high doses of ICS/LABA, which would be step 4. These are described in the next section (Stepping Down from Step 4 Therapy). Overall, the data from these studies show that patients treated with moderate- to high-dose ICS/LABA experience better asthma control when stepping down to a combination product with a lower ICS dose than when the LABA is discontinued.^{37,39,45,46} Whether that applies to patients with less severe disease requires further study.

Table 3
ICS/LABA Combination Products Approved to Treat Asthma in the United States^a

ICS/LABA	Formulation (μg)	Indicated dosing	Age	Range for possible daily dosing ^b
Fluticasone propionate/ Salmeterol (Advair Diskus)	100/50	1 inhalation twice daily	≥12 years	100/50 μg to 1000/100 μg
	250/50			
Fluticasone propionate/ Salmeterol (Advair HFA)	500/50	1 inhalation twice daily	≥4 years to 11 years	100/50 μg or 200/100 μg
	100/50			
	45/21	2 inhalations twice daily	≥12 years	100 μg to 920/84 μg
	115/21			
Budesonide/ formoterol (Symbicort)	230/21	2 inhalations twice daily	≥12 years	80/4.5 μg to 640/18 μg
	80/4.5			
	160/4.5	2 inhalations twice daily	≥6 years to <12 years	80/4.5 μg to 320/18 μg
Fluticasone furoate/ vilanterol (Breo Ellipta)	80/4.5			
	100/25	1 inhalation once daily	≥18 years	100/25 μg or 200/25 μg
	200/25			
Mometasone furoate/ formoterol (Dulera)	100/5	2 inhalations twice daily	≥12 years	100/5 μg to 400/20 μg
	200/5			

Abbreviations: ICS, inhaled corticosteroids; LABA, long-acting beta-agonist.

^aThe starting dose for each depends on the patient's asthma severity.

^bMay include doses that are not indicated.

Most studies evaluating step-down therapy have not categorized subjects according to guideline-based severity. One study that did compare the 2 step-down strategies in patients with guideline-defined mild-to-moderate asthma reported better asthma control when patients were maintained on combination treatment.⁴⁷ The 752 subjects (16–79 years old) included in this double-blind, placebo-controlled study were considered stable on budesonide/formoterol 160 μg/9 μg twice daily. Twelve weeks of treatment with the combination at the same twice-daily dose was compared with once-daily evening dosing with budesonide/formoterol 320 μg/9 μg, budesonide/formoterol 160 μg/9 μg, budesonide 320 μg, or placebo. Those treated with the budesonide/formoterol combination, regardless of dosing regimen, showed better maintenance of asthma control compared with budesonide monotherapy or placebo as measured by evening peak expiratory flow rate (PEF, primary outcome), symptoms, and nighttime rescue medication use.⁴⁷ Some differences favoring twice-daily dosing were reported, particularly for evening measurements (ie, at the end of the daily treatment period), suggesting that patients who reduce therapy to a once-daily dose may need to be more carefully monitored. In this study, exacerbations were included as part of the safety results and not efficacy. Clinical asthma exacerbations occurred in significantly fewer subjects treated with budesonide 320 μg—as monotherapy or as part of a combination regimen—compared with placebo.⁴⁷

Loss of asthma control after stopping combination therapy was reported in an earlier study in 647 subjects who were considered stable while using FP/salmeterol 100 μg/50 μg twice daily.⁴⁸ The subjects were randomized to 16 weeks of treatment with the same combination therapy or its individual components—FP 100 μg or salmeterol 50 μg twice daily—or to treatment with montelukast 10 mg once-daily or placebo. Compared with continuing the combination therapy, asthma control measured by morning PEF (primary outcome), symptoms, nighttime awakenings, and rescue medication use deteriorated in all of the step-down arms.⁴⁸ Exacerbations, again recorded as adverse events, occurred in 2%, 8%, 23%, and 11% of the subjects receiving FP/salmeterol, FP, salmeterol, and montelukast, respectively. Although the patients were not assigned a guideline-

based severity level at screening, a post-hoc analysis compared subjects with normal lung function (ie, FEV₁ ≥ 80% of predicted) with those having FEV₁ < 80% of predicted at baseline. The clinical outcomes were comparable.

In many of the step-down studies, individual patients whose asthma symptoms were controlled on ICS/LABA were able to step down to ICS alone without compromising symptom control. Although much of the reported data involve subjects using moderate-to-high doses of ICS/LABA, one 20-week study compared asthma control after LABA withdrawal in patients who had been maintained on combinations with an ICS dose of > 400 μg/day budesonide-equivalent (n = 29) and those using ≤ 400 μg/day (n = 27).⁴⁹ In this study treatment was continued until exacerbation, defined as any of the following: 2 consecutive nights with waking due to asthma; 3 consecutive days with PEF less than 3 standard deviations from the run-in value; 3 consecutive days with bronchodilator use greater than once-per-day; the subject reporting that his or her asthma symptoms had increased.

After a 2-week run-in, LABA was discontinued, and the subjects used only their previous dose of ICS for 6 weeks. Fifty-one subjects completed LABA discontinuation. For the next 6-week interval, 26 subjects who had been using more than 400 μg/day budesonide-equivalent halved their ICS dose, and 25 who were using 400 μg/day or less budesonide-equivalent discontinued their ICS. Twenty-one of the 26 subjects remained stable after halving their ICS dose, and for the final 6 weeks they discontinued ICS. At trial end, 25 were stable despite LABA and ICS withdrawal.⁴⁹

A substantial proportion of subjects tolerated both LABA withdrawal and ICS dose reduction, which may support the hypothesis that for patients with well-controlled asthma, therapy can often be reduced. However, the fact that almost 45% of the subjects were able to completely stop treatment for 6 to 12 weeks raises the question of whether the subjects had been overtreated. Patients being stepped up in therapy after a period of inadequate control, but then not stepped down even after control has been reestablished and maintained over time, is not uncommon.^{12,13} That the patient's level of severity before step-down was not captured, nor

Table 4
ICS/LABA Studies Comparing Stepping Down with Lower Doses of ICS/LABA or ICS Monotherapy

Author, year	Design	Subjects, (age range, years)	Pre-study dose of ICS/LABA (μ g)	Study duration (weeks)	Step-down	Primary outcome	Secondary outcomes and comments
Bateman et al, 2006 ⁵⁷	RDBPG	n = 435 (12–80 years)	FP/SAL (250/50 μ g BID) for 12 weeks (most subjects had used ICS/LABA $\geq$ 1000 μ g BDP equivalent before study)	12 (2-week run-in)	FP/SAL 100/50 μ g BID or FP 250 μ g BID	Change in mean am PEF: FP/SAL, -0.3 L/min; FP, -13.2 L/min ($P < .001$)	%Subjects well-controlled (based on composite Sx-related scores): FP/SAL, 86%; FP, 79% %Subjects totally controlled: FP/SAL, 56%; FP, 48% Odds of being well controlled were 46% greater with FP/SAL than FP alone (OR, 1.46; 95%CI, 0.96–2.23; $P = \text{NS}$); odds of being totally controlled were 62% greater (OR, 1.62; 95%CI, 1.09–2.40; $P = .017$)
Godard et al, 2008 ⁵⁶	RDBPG	n = 476 (18–81 years)	FP/SAL 250/50 μ g BID for 8 weeks (most subjects had used ICS/LABA $\geq$ 1000 μ g BDP equivalent before study)	24 (8 week run-in)	FP/SAL 250/50 μ g BID; FP/SAL 100/50 μ g BID; or FP 250 μ g BID	Change in mean am PEF at week 12: FP/SAL 250/50, 1.76 L/min; FP/SAL 100/50, -3.07 L/min; FP 250, -16.51 L/min ($P < .0001$ vs FP/SAL 250/50)	FP/SAL 100/50 maintained am and pm PEF over wk 13–24 comparable to FP/SAL 250/50, but both decreased with FP 250 Fewer moderate exacerbations (treated with OCS) with FP/SAL vs FP
Koenig et al, 2009 ⁴⁸	RDBDDPG	n = 647 ($\geq$ 15 year)	BDP 160–420 μ g/d or BUD 200–400 μ g/d or FLU 1000 μ g/d or FP MDI 176–220 μ g/d or FP DPI 200 μ g/d or TAA 600–1000 μ g/d for $\geq$ 4 weeks	16 (2-week run-in)	FP/SAL 100/50 μ g BID (n = 172); FP 100 μ g BID (n = 159); SAL 50 μ g BID (n = 152); Montelukast, 10 mg QD (n = 164)	Asthma control measured by am PEF deteriorated in all of the step-down arms	Asthma control measured by Sx, nighttime awakenings, and rescue medication use deteriorated in all step-down arms
Berger et al, 2010 ⁴⁷	RDBDDPC	n = 752 (16–79 years)	BUD/FOR 160/9 μ g BID for 4–5 weeks	12 (4–5 week run-in)	BUD/FOR 160/9 BID, BUD/FOR 320/9 QD, BUD/FOR 160/9 QD, BUD 160 QD, or placebo	Mean pm PEF: all BUD/FOR doses were significantly more effective than placebo or BUD alone ($P < .001$ for both)	Asthma control measured by DT and NT asthma Sx scores, NT awakenings due to asthma, rescue medication use was greater in the BUD/FOR groups vs BUD alone; number of withdrawals because of decreased asthma control was lower in the combination arms than either placebo or BUD ($P < .001$ for both)

Reddel et al, 2010 ⁶⁵	RDBPG	n = 82 (18-80 years)	FP/SAL 500/50 µg BID ≥ 4 weeks (most subjects had used ICS/LABA ≥ 2000 µg BDP equivalent before study)	56 (4 week run-in)	FP/SAL 500/50 µg BID or FP 500 µg BID for 12 weeks, then down titration possible at 8 weekly intervals: FP/SAL 250/50 µg BID, 100/50 µg BID, 100/50 µg QD, 0; FP 500 µg BID, 250 µg BID, 100 µg BID, 100 µg QD, 0	Final dose of FP: FP/SAL, (-27.9%); FP, 816 µg (-18.4%)	Moderate exacerbations (treated with double study medication) were lower with FP/SAL ($P < .001$) No significant between-group differences in measures of asthma control (ACQ), QoL, clinic lung function, airway inflammation am and pm PEF higher with FP/SAL ($p < 0.001$ both).
Papi et al, 2012 ⁷⁶	RCOLPG	n = 440 (18-65 years)	FP/SAL 1000/100 µg ≥ 8 weeks	32 (8 week run-in)	FP/SAL 250/50 µg, 1 inhalation BID or eBDP/FOR 100/6 µg, 2 inhalations BID	Change in mean am PEF: No between-treatment differences	% Patients with asthma control (GINA composite score); controlled asthma: FP/SAL, 85.2%; eBDP/FOR, 90.0% partly controlled asthma: FP/SAL, 9.2%; eBDP/FOR, 6.0% Exacerbations: FP/SAL, 14.6%; eBDP/FOR, 18.0%
Adachi et al, 2016 ⁷¹	RCOLPG	n = 430	FP/SAL 250/50 µg BID ≥ 4 weeks	25 (4 week run-in)	FF/VIL 100/25 µg for 8 weeks (period 1) then FF 100 µg QD or FP 100 µg QD or FP 250 µg BID for 12 weeks (period 2)	Time to withdrawal because of poorly controlled asthma requiring step-up therapy and proportion of subjects with well-controlled asthma at trial end (co-primary variables): No significant between-Tx differences for either	Period 1: Lung function (FEV ₁ , PEF) and ACT remained stable Period 2: ACT remained stable in all groups, but reductions in trough FEV ₁ (105-135 mL) and PEF (18.1-21.3 L/min) were noted
Akashi et al, 2016 ⁷⁰	RCOLPG	n = 128 (5-15 years)	FP/SAL 100/50 µg BID ≥ 12 weeks	12	FP/SAL 50/25 µg BID or FP 100 µg BID	Change in %predicted PEF: FP/SAL remained stable; FP decreased slightly ($P = .01$ week 8, $P = .05$ week 12, vs BL)	No between-Tx differences in measures of asthma control (c-ACT), airway inflammation Measures of lung function declined with FP monotherapy
Koskela et al, 2016 ⁴⁹	RCOLPG	n = 56 58.8 ± 11.7 year	ICS/LABA combination with either ICS > 400 µg/d (n = 29) or ≤ 400 µg/day (n = 27) BUD equivalent	20 (2 week run-in)	1 st 6 weeks: LABA stopped 2 nd 6 weeks: > 400 µg/d BUD equivalent halved ICS dose; ≤ 400 µg/day BUD equivalent stopped ICS Final 6 weeks: All subjects stopped ICS	Exacerbation, defined as 2 consecutive nights with wakening because of asthma or 3 consecutive days with PEF < 3 standard deviations from run-in or 3 consecutive days with bronchodilator use > once-a-day or the subject reporting that his/her asthma Sx increased: No exacerbations: Initial LABA discontinuation, n = 51; >400 µg/day BUD equivalent halved ICS dose at 6 weeks, n = 26; ≤400 µg/day BUD equivalent stopped ICS at 6 weeks, n = 25; after ICS and LABA discontinued, final visit, n = 25	ACQ score < 0.29, ACQ without spirometry < 0.15, and FEV ₁ > 96% of predicted, considered predictive of a successful outcome after step-down That 45% of subjects were able to completely stop treatment for 6-12 weeks raises question of whether the subjects had been over-treated
Mori et al, 2016 ⁶⁹	RCOLPG	n = 91 (44-69 years)	BUD/FOR 320/9 µg BID ≥ 12 weeks	12	BUD/FOR 160/4.5 µg BID or BUD 400 µg BID	Incidence of asthma exacerbations: BUD/FOR, 16.4%; BUD, 12.5% ($P = NS$)	No between-Tx differences in measures of asthma control (ACQ5, ACT), airway inflammation (FeNO), or lung function

(continued on next page)

Table 4 (continued)

Author, year	Design	Subjects, (age range, years)	Pre-study dose of ICS/LABA (μg)	Study duration (weeks)	Step-down	Primary outcome	Secondary outcomes and comments
Usmani et al, 2017 ¹⁴	RCOL, pragmatic trial	n = 225 (18–75 years)	FEV ₁ FP/SAL 500/50 μg BID $\geq$ 6 months	24	Phase 1 (12 weeks): FP/SAL 500/50 μg BID or FP/FOR 500/10 μg BID Phase 2 (12 weeks): FP/FOR 500/10 μg BID or FP/FOR 250/10 μg BID	Asthma control (ACQ7): No between-group differences determined for either phase	No significant between-group differences in either phase for measures of QoL, Sx, lung function, or exacerbations In phase 1, odds of being more controlled according to GINA criteria were higher with FP/FOR 250/10 μg BID (OR: 2.00; 95%CI, 1.14–3.52; $P = .016$); no between-Tx difference for odds in phase 2
Rogers et al, 2018 ³³	RDBPG	n = 459 (17–51 years)	FP/SAL 250/50 μg BID $\geq$ 4 weeks	56 (8 weeks run-in)	FP/SAL 250/50 μg BID OL for 8 weeks then FP/SAL 250 μg BID, FP/SAL 100 μg BID, FP 250 μg BID for 48 weeks	Time to Tx failure (broadly defined ^a): %Subjects with Tx failure by trial end: FP/SAL 250/50, 26%; FP/SAL 100/50, 28%; FP 250, 31% Time to Tx failure did not differ between FP/SAL 100/50 and FP 250; insufficient evidence to determine noninferiority vs FP/SAL 250/50	No between-group differences in asthma control (ACT and the Asthma Symptom Utility Index)

Abbreviations: ACQ#, Asthma Control Questionnaire (# = number of items); ACT, Asthma Control Test; am, morning; BDP, beclomethasone dipropionate; bid, twice per day; BL, baseline; BUD/FOR; budesonide/formoterol combination; CI, confidence interval; eBDP/FOR, extrafine beclomethasone/formoterol combination; FEV₁, forced expiratory volume in 1 second; FP/SAL, fluticasone propionate/salmeterol combination; ICS, inhaled corticosteroid; LABA, long-acting beta₂-agonist; μg , microgram; N, number of subjects; NS, not significant; OR, odds ratio; PEF, peak expiratory flow; QoL, quality of life; RDBDDPC, randomized double-blind double-dummy placebo-controlled; RDBPC, randomized double-blind placebo-controlled; RDBPG, randomized double-blind parallel-group; RCOL, randomized controlled open-label; RCOLPG, randomized controlled open-label parallel-group; Sx, symptom(s); Tx, treatment(s).

^aHospitalization or urgent care visit for asthma; systemic corticosteroids for asthma; increase in controller therapy; decrease in prebronchodilator FEV₁ $\geq$ 20% below randomization value; 2 consecutive days with a 35% decrease in am PEF from BL; > 10 puffs of rescue beta₂-agonist for 2 consecutive days; refusal to continue (eg, medication intolerance; inadequate symptom relief); physician's judgment (reasons of safety).

was it prospectively confirmed that step 3 (or step 4) therapy was necessary before step-down, is complicating. Whether patients stepping down from lower doses of ICS/LABA (eg, step 3) would be more successful than those stepping down from higher doses (eg, step 4), assuming similar levels of asthma control, remains unclear.

Patients Using ICS Monotherapy

In stepping up ICS monotherapy from step 2 to step 3, current guidance suggests doubling the dose of ICS.^{1,3,4} For stepping down ICS monotherapy, the recommendation is reversed: reduce the ICS dose by 50%.^{1,2} What may seem to be a rather dramatic single-step reduction is supported by limited data.^{7,50–52} Alternatively, consideration may be given to using once-daily ICS/LABA with a lower dose (50%) of ICS than the monotherapy.^{19,23–26,40} Unfortunately, the studies cannot be directly compared because of differences in design, outcome measures, and definition of control. A systematic review of the literature on stepping down the dose of ICS, with or without LABA, concluded that the current evidence is not sufficient to determine whether patients can maintain asthma control while reducing their ICS dose or whether decreasing the dose of ICS reduces harm in terms of fewer side effects.⁵³ Larger and longer studies are needed in the appropriate patients for all step-down strategies at this level, including studies of predictors of success with different step-down choices.

Patients Using ICS and Leukotriene Modifier (LM)

Some patients at step 3 may be using ICS + LM, and stepping down might proceed by either decreasing the dose of ICS, discontinuing the LM, or both. Discontinuing the ICS is not recommended because evidence shows an association with an increased risk for exacerbation.^{15,19,54,55} Markers of inflammation may aid in proper patient selection,^{56–61} but further studies are needed.

Immunotherapy

For patients with allergic asthma, immunotherapy may be helpful to further reduce the dose of ICS. A systematic review of 6 studies in patients allergic to house dust mite or birch pollen reported that for patients using a medium dose of ICS (GINA steps 3,4), a 50% reduction in ICS dose was more likely when treatment included immunotherapy.⁶² More data are needed for different types of allergens.

Summary and Recommendations

The data are limited for how to step-down therapy for a patient whose condition is well controlled at the step 3 level. Minimizing the dose of ICS to reduce the potential for adverse effects is a priority, and the authors recommend the strategy that permits control at the lowest dose of ICS for the patient. A combination of approaches may be needed to step-down the patient to the least amount of medication that controls symptoms, maintains lung function, and minimizes risk, and the process of stepping down may be better served by a series of gradual steps with demonstrated periods of disease control between.

For most patients at this level, stepping down to a low-dose ICS/LABA may permit lower ICS exposure while maintaining asthma control. This is true even for patients previously maintained on ICS monotherapy. Low-dose budesonide/formoterol as maintenance and reliever medication have been shown to improve asthma control as measured by symptoms, lung function, and exacerbations compared with a higher dose of budesonide alone or the combination, both with a SABA reliever.^{1,20–23,63} This approach has not received FDA approval, although it has been approved by the

European Medicines Agency. Similar data for other ICS/LABA combinations are limited, and an as-needed SABA is recommended with those agents as directed by current guidelines.^{1,2,19} For patients with mild asthma, as-needed budesonide/formoterol has been shown to reduce exacerbations, maintain lung function, and enhance patient satisfaction and adherence (as previously described), providing indirect evidence for another potential strategy for stepping down therapy, particularly in patients who may not be adherent with regular maintenance therapy.^{23–26,64}

The authors recommend the following when stepping down from step 3 to step 2 therapy:

- For patients using an ICS/LABA combination, there is some flexibility in stepping down, which may be achieved by:
 - Decreasing the dose of the ICS component by changing the number of puffs or the frequency of dosing (though these may not be FDA-approved dosing options)¹
 - Switching to a combination product with a lower ICS dose (Table 3)
 - Discontinuing the LABA while maintaining the ICS dose; this strategy may be appropriate for some patients, particularly those sensitive to the side effects of the bronchodilator; consideration can then be given to carefully tapering the dose of ICS
- For patients using ICS+LM, consider stopping the LM before decreasing the dose of ICS
- For patients using ICS only, decrease the dose of ICS
 - Consider a step-down to a low-dose ICS/LABA, which may permit lower ICS exposure while maintaining asthma control
 - Low-dose budesonide/formoterol as maintenance and reliever medication may be appropriate for some patients (not an FDA-approved approach)
- For patients with allergic asthma, immunotherapy may help further reduce the dose of ICS

Stepping Down from Step 4 Therapy

A step-down from step 4 therapy (Fig 1) may be considered for the patient who has achieved and maintained control as previously described (eTable 1) with appropriate maintenance treatment.^{3,4} When considering a step-down in therapy, the patient should be assessed for the duration of asthma control, including exacerbations in the previous year and other factors that might limit success (Table 2), such as adherence to the treatment plan, adequacy of inhalation technique, and previous allergic and seasonal trigger patterns. The medical history should also be reviewed for the timing of previous steps-up and corresponding responses to each.

The length of time control should be maintained before stepping down therapy is not clear. Current guidelines suggest 3 months,^{1,2} and most studies of ICS/LABA step-down have required at least 12 weeks of demonstrated control before randomization (Table 4). However, data suggest that, at this level of severity, patients with a longer period of control are more successful when step-down is attempted. A recent prospective study reported that disease stability for 3 months may not be sufficient to optimally predict the success of tapering from high-dose to medium-dose ICS/LABA. The study found that despite asthma stability for 3 months, patients with more exacerbations in the prior year experienced significantly more asthma exacerbations during step-down than those maintained on the high-dose combination. These findings caution clinicians to strongly consider increasing the time to start stepping

down high-dose ICS/LABA in those patients with a history of prior year asthma exacerbations.¹⁴

Patients Using Moderate-High Dose ICS/LABA

At step 4, most patients are using medium or high doses of an ICS/LABA combination, and the options for stepping down are similar to those described for step 3: either 1) keeping the patient on a combination product, but at a lower dose of ICS; or 2) discontinuing the LABA with or without reducing the dose of ICS. This is evident in the studies evaluating protocols for stepping down from ICS/LABA (Table 4). Many did not discriminate between guideline step levels 3 and 4 and included subjects at both levels of severity. Nonetheless, based on the data and their clinical experience, the authors do not support discontinuing the LABA for the patient at step 4. Continuing the LABA with a lower dose of ICS has been shown to be more likely to better maintain the patient's asthma status based on lung function and asthma control measures, with the added benefit of potentially allowing a greater decrease in ICS dose.^{65–68}

This was the conclusion of a study comparing gradual ICS dose reduction over time in patients whose conditions had been controlled for at least 6 months on high-dose ICS/LABA (2000 µg/day beclomethasone-equivalent).⁶⁵ Eighty-two subjects were randomized to FP/salmeterol 500 µg/50 µg twice daily or FP 500 µg twice daily, with assessment for down-titration of FP at 8-week intervals to 250 µg twice daily, 100 µg twice daily, 100 µg daily, and 0 µg given alone or in combination with salmeterol (maintained at 50 µg).⁶⁵

Over the course of the study, the dose of FP decreased by 27.9% in the combination group (from 1000 µg to 721 µg) and by 18.4% with FP monotherapy (from 1000 µg to 816 µg); the minimum effective doses of FP were 534 µg and 724 µg, respectively (OR, 3.37, $P = .005$). Morning and evening PEF values were higher in the combination group ($P < .001$, both), as was evening forced expiratory volume in 1 second (FEV₁, $P = .049$). Exacerbations—both moderate (treated with double study medication) and severe (treated with oral corticosteroid, OCS)—were lower in the combination group but only reached statistical significance for moderate exacerbations ($P < .001$). Trends suggesting better asthma control and quality of life with combination treatment were observed.⁶⁵

Similar outcomes were reported for 2 earlier noninferiority studies of shorter duration in patients who had been using high-dose ICS/LABA, defined as 1000 µg beclomethasone-equivalent per day.^{66,67} A 6-month trial included 476 subjects deemed “well controlled” during the last 2 weeks of an 8-week, open-label, run-in period during which they were treated with FP/salmeterol 250 µg/50 µg twice daily.⁶⁶ A 3-month study evaluated 435 subjects whose asthma was similarly deemed “well controlled” during the last 4 weeks of a 12-week open-label period.⁶⁷ The subjects were randomized to 3 groups for 24 weeks⁶⁶ or 12 weeks⁶⁷: 1) FP/salmeterol 250 µg/50 µg, 2) FP/salmeterol 100 µg/50 µg, or 3) FP 250 µg, all given twice daily. In both studies, the combination products maintained the subjects' lung function and asthma control status, whereas deterioration in these outcomes was observed in the groups using FP monotherapy.

Two systematic reviews that evaluated stopping LABA in adults (≥ 18 years old)⁴⁴ and in adults and older children (≥ 15 years old)⁶⁸ whose conditions were well controlled by ICS/LABA combination therapy also concluded that stopping LABA could increase asthma-related impairment. However, the analyses were limited by differences in study designs, initial dosing at screening, patient population, and trial duration.

In each of the studies, some patients were able to step down to ICS monotherapy without loss of asthma control. Whether this represented a true step-down is not clear, because the studies did not document the need for combination therapy before

randomization, such that for some patients, the step-down to monotherapy might be reflective of overtreatment. Subsequently, 2 studies—1 in adults⁶⁹ and 1 in children⁷⁰—comparing these step-down approaches suggested that either may be acceptable. Both studies used a prospective, open-label, randomized, parallel-group design in which subjects were assigned to 12 weeks of treatment with either half the dose of the ICS/LABA or to ICS monotherapy at approximately the same dose as the ICS in the combination.

Ninety-one adults who demonstrated good asthma control while using budesonide/formoterol 320 µg/9 µg twice daily for at least 3 months were randomized to budesonide/formoterol 160 µg/4.5 µg or budesonide 400 µg (or equivalent), both given twice per day.⁶⁹ The incidence of exacerbations (primary outcome) was similar between the 2 groups over the 12 weeks of treatment, and measures of asthma control (Asthma Control Test, ACT; Asthma Control Questionnaire, ACQ) and airway inflammation (FeNO) remained stable. However, subjects using ICS alone showed a slight, but statistically significant, decline in lung function measured as FEV₁ ($P = .001$, week 12 vs baseline).⁶⁹

Similar results were reported for the pediatric study, which included 128 children (5–15 years old) who showed good asthma control for at least 3 months while using FP/salmeterol 200 µg/100 µg/day (given as 50 µg/25 µg, 2 puffs twice daily) and were randomized to FP/salmeterol 50 µg/25 µg or FP 100 µg, both given twice daily.⁷⁰

In another study, 430 subjects considered well controlled on FP/salmeterol 250 µg/50 µg twice-daily were switched to once-daily fluticasone furoate (FF) 100 µg/vilanterol 25 µg for 8 weeks, and those who maintained control ($n = 371$) were then randomized to monotherapy with FF 100 µg once daily, FP 100 µg twice daily, or FP 250 µg twice daily for 12 weeks.⁷¹ No significant between-treatment differences were determined for the time to withdrawal because of poorly controlled asthma requiring step-up therapy or the proportion of patients with well-controlled asthma at the end of treatment (co-primary variables), although again, lung function slightly declined across all 3 ICS monotherapies compared with the combination.⁷¹

In contrast, both lung function and asthma control remained stable for 57 patients whose conditions were considered well controlled on either budesonide 320 µg/formoterol 9 µg twice daily or FP 250 µg/salmeterol 50 µg twice daily who were stepped down to ICS monotherapy with ciclesonide 320 µg once daily for 12 weeks.⁷² Some variability in lung function was reported, however, for 44 patients who were stepped down to budesonide 200 µg twice-daily, but whether this reflected the specific steroid or better adherence to once-daily treatment is unclear.⁷²

None of these studies documented a need for moderate-dose combination therapy in the subjects before baseline, so whether reduction in treatment reflected a satisfactory step-down or previous overtreatment cannot be determined. A related question is whether 12 weeks of asthma control after a step-down in therapy is clinically relevant, particularly if the patient had required moderate-to-high doses of a combination product. More recently, Rogers et al³³ conducted a 56-week randomized, double-masked, 3-arm study comparing step-down approaches for patients (≥ 12 years old) considered well controlled on “moderate-dose” ICS/LABA (defined as FP 250 µg/salmeterol 50 µg twice daily) for at least 30 days. A total of 459 patients whose asthma remained stable on the moderate-dose ICS/LABA during an 8-week, open-label, run-in period were randomized to continue their twice-daily treatment with FP/salmeterol or switched to either FP 100 µg/salmeterol 50 µg twice daily or FP 250 µg twice daily monotherapy for 48 weeks.

In this study, stable asthma was defined as an ACT score of 20 or more at weeks 4 and 8, no unscheduled care encounters for asthma, no change in asthma medication, prebronchodilator FEV₁ $\geq 70\%$ predicted, < 16 puffs of rescue SABA/week (and no more than 10

Table 5

Studies Reporting Complications and Burden from Chronic Oral Corticosteroid (C-OCS) Use in Prednisone Equivalency among Asthma Patients

Author, year	Design and Asthma cohort	Subjects (mean age, years)	C-OCS defined	Groups compared	Significant adverse comorbidities related to C-OCS use	Significant asthma burden associated with C-OCS use	Baseline predictors ^a for increase in future year C-OCS use or OCS adverse effects	Other significant findings
Lefebvre et al, 2015 ⁸³	Retrospective observational Medicaid claims data 1997-2013	n = 3628, ≥12 years with persistent asthma + OCS >6 months (57.6 ± 16.3)	>6 mg/day	>6-12 mg/day (medium) and >12 mg/day (high) vs ≤6 mg/day (low)	Infections GI illnesses Bone muscle CVD Metabolic Psychiatric Ocular	NR	NR	Higher annual incremental costs relative to low OCS (high OCS, \$5479; medium OCS, \$1194) associated with more ED visits (by 78%, for high, medium) in-patient visits (by 59%, 25% for high, medium), and pharmacy claims (by 35%, 25% for high, medium)
Zazzali et al, 2015 ⁸⁴	Matched cohort retrospective observational claims data 2008-2009	n = 3972, ≥18 years with ≥2 asthma medical claims + ≥2 asthma medications; no COPD (54.4 ± 12.7)	≥30 days supply/year	≥30 days (median dose 1.26 g) vs <30 days (median dose 0.25 g) supply/year	Infections Osteoporosis Fractures Pneumonia Hypertension Diabetes Obesity Lipid disorders	NR	NR	None
Dalal et al, 2016 ⁸⁷	Propensity matched retrospective observational claims data 2003-2014	n = 12,697/ group, ≥12 years with ≥ 2 asthma medical claims (62±62)	≥5 mg/day for ≥6 months	≥5 mg/day for ≥6 months vs no OCS	Infections GI diseases Bone/muscle CVD Metabolic Psychiatric Skin disorders Eye diseases	NR	NR	Higher overall annual health care resource use and costs for C-OCS complications (\$4639)
Sweeney et al, 2016 ⁹⁰	Cross-sectional observation of British Thoracic Difficult Asthma Registry	n = 770, >12 years with severe asthma	Required daily OCS	Daily (n = 328) vs not daily OCS (n = 442)	DM2 Hypertension High cholesterol Fracture Obesity Obstructive sleep apnea Cataracts Peptic disease Depression Skin diseases Cushingoid Adrenal insufficiency	Lower: Spirometry AQLQ More: SABA ICS ED/hospital visits	NR	More OCS comorbidities with OCS dependency

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Table 5 (continued)

Author, year	Design and Asthma cohort	Subjects (mean age, years)	C-OCS defined	Groups compared	Significant adverse comorbidities related to C-OCS use	Significant asthma burden associated with C-OCS use	Baseline predictors ^a for increase in future year C-OCS use or OCS adverse effects	Other significant findings
Zeiger et al, 2017 ⁸²	Retrospective observational administrative data 2010–2012	n = 9546, 18–64 years meeting HEDIS persistent asthma 2-year criteria in MCO (46.0±12.7)	≥2.5 mg/day/year (8.2% of cohort)	≥2.5 mg/day/year vs <2.5 mg/day/year	CS poisoning Obesity Cataracts Osteoporosis Fractures Hypertension Infections Anxiety Ulcer disease	More or higher: GINA stepcare Controller use Asthma specialty care Excess SABA Asthma exacerbations ED/hospital visits Blood eos Eczema Rhinitis GERD Pneumonia Chronic sinusitis	C-OCS Nasal polyps Asthma specialist care GINA step 4–5 Theophylline use Increasing age Blood eos ≥ 150 cells/mm ³ Females	Findings similar with C-OCS defined as ≥4 courses / year (4.8%) Increased burden with increasing OCS dose
Barry et al, 2017, ⁸⁸ 2018 ⁸⁶	Retrospective observational matched administrative data 2000–2017	n = 7195, >12 years: 808 with severe asthma; 3975 with mild-moderate asthma; 2412 with no asthma but rhinitis	High-dose OCS (median 3.9 g over 2 years); low-dose OCS (median, 0.25 g over 2 years)	High-dose vs low-dose OCS	Female > Males (OR): DM2 (1.5) Obesity (1.4) Osteoporosis (5.2) Osteopenia (5.3) Hypertension (1.4) Kidney disease (1.8) Dyspeptic (4.0) Psychiatric (1.4) Sleep disorders (1.7) Cataracts (1.9) CVD (1.4) Fracture (1.5) Bone-related Peptic disease Severe infections Herpes zoster DM2 Cataract Affective disorders CVD	NR	NR	Age-related differences in C-OCS comorbidities noted: > nondrug costs for females based on C-OCS use
Bloechliger et al, 2018 ⁸⁹	Retrospective observational administrative data with matching 2000–2015	n = 269,368, ≥18 years with persistent asthma (≥ GINA Step-2)	Various methods (dose ever, dose last 2 years, courses/ year)	Dose: <500 mg vs. 500–1000 mg, or >2000 mg ever Courses 1, 2–3, ≥4 per year	Bone-related Peptic disease Severe infections Herpes zoster DM2 Cataract Affective disorders CVD	NR	NR	Possible dose response of ever OCS (<500 mg, 500–1000 mg, >2000 mg) for bone-related conditions, severe infections, cataract, affective disorders, DM2, CVD
Sullivan et al, 2018 ⁸⁵	Retrospective observational claims data 2000–2014	n = 228,436, ≥18 years with ≥2 asthma outpatient medical claims or ≥1 primary asthma ED or inpatient claim	≥4 courses/year	OCS, n = 72,063 vs no OCS n = 156,373 with propensity score matching	Osteoporosis Hypertension Obesity DM2 GI ulcers/bleeds Fractures Cataracts	ED Inpatient ≥7 SABA canister/year Obesity DM2	Increased risk for new OCS morbidity: Current OCS Prior year OCS Total year with OCS	Possible dose response with increased courses of OCS

Abbreviations: AQLQ, asthma quality of life questionnaire; C-OCS, chronic oral corticosteroids; CVD, cardiovascular disease; DM2, diabetes mellitus type 2; ED, emergency department visit; GI, gastrointestinal disease; GINA = Global Initiative for Asthma; ICS, inhaled corticosteroid; MCO, managed care organization; N, number of subjects; NR, not reported; OCS, oral corticosteroids; SABA, short-acting beta₂-agonist.

^aMultivariable analyses.

Table 6

Representative Randomized Double-Blind Placebo Controlled or Comparator Studies Reporting Reduction in Chronic Oral Corticosteroid (OCS) Use with Inhaled Corticosteroids (ICS) in Severe Asthma

Author, year	Design	Subjects, mean age, years (Range)	Treatments, dose	Duration (weeks)	Controllers other than indicated treatments at baseline	Baseline OCS mg/day (prednisone equivalent)	Outcomes
Laursen et al, 1986 ¹⁰³	DB, active comparator	n = 50 (17–73 years)	BID dosing: BUD 800 μ g (high-dose, n = 25); BUD 200 μ g (low-dose, n = 25)	15	Theophylline, cromolyn (continued during study)	High-dose ICS: 14.0 $\pm$ 1.3 mg; Low-dose ICS: 13.9 $\pm$ 1.2 mg	Final OCS dose: High-dose ICS, 6.5 $\pm$ 0.6 mg/day, 54% reduction; Low-dose ICS, 8.5 $\pm$ 1.2 mg/day 39% reduction ($P < .05$)
Lacronique et al, 1991 ⁹⁷	DBPC	n = 124 (52 $\pm$ 11.5 years)	QID dosing: BDP 250 μ g (n = 63); placebo (n = 61)	12	Theophylline (continued during study)	BDP: 17 $\pm$ 7.5 mg; Placebo: 15.6 $\pm$ 7.7 mg	%Subjects discontinued OCS: BDP: 76%, final dose OCS = 3.1 $\pm$ 7.4 mg/day; Placebo: 34%, final dose OCS = 9.1 $\pm$ 9.4 mg/day ($P < .001$) Spirometry: BDP > placebo ($P < .001$)
Hummel And Lehtonen, 1992 ¹⁰⁴	DB, active comparator	n = 143 (18–65 years)	TID dosing: BDP 500 μ g (n = 71); BDP 100 μ g (n = 72)	24	Theophylline, cromolyn (continued during study)	10–40 mg	Reduction of 5 mg in both groups
Noonan et al, 1995 ⁹⁸	DBPC, stratified by OCS and ICS at BL	n = 96 ($\geq$ 12 years)	BID dosing: FP 1000 μ g (n = 32); FP 750 μ g (n = 32); placebo (n = 32)	16	Other ICS (discontinued during study)	5–20 mg daily or 10–40 mg every other day	%Subjects discontinued OCS: High-dose FP, 88%; Medium-dose FP, 69%; placebo, 3% ($P < .001$ vs placebo both FP doses) Spirometry improved both FP doses vs placebo ($P < .05$)
Nelson et al, 1998 ¹⁰⁰	DBPC	n = 159 (20–69 years)	BID dosing: BUD 800 μ g (n = 53); BUD 400 μ g (n = 53); placebo (n = 53)	20	Other ICS (converted to prednisone equivalent at study start)	High-dose: 19.5 mg Medium-dose: 19.7 mg; Placebo: 18.7 mg	%Subjects reduced/discontinued OCS: High-dose BUD, 79%/64%, final dose OCS = 4.4 mg; Medium-dose BUD, 82.9%/68%, final dose OCS = 3.5 mg; Placebo, 27%/8%, final dose OCS = 13.1 mg ($P < 0.001$ vs placebo, both BUD groups)
Nelson et al, 1999 ⁹⁹	DBPC	n = 111 (12–77 years)	BID dosing: FP 1000 μ g (n = 36); FP 500 μ g (n = 41); placebo (n = 34)	16	LABA, theophylline (continued during study)	5–40 mg daily or 10–80 mg every other day	%Subjects discontinued OCS: High-dose FP, 89%; Medium-dose FP, 75%; Placebo, 9% ($P < .001$ vs placebo both FP groups) Significant improvements in spirometry, Sx, SABA more often with high-dose FP
Sheikh et al, 2000 ¹⁰¹	OL	n = 8 (11.6 years; (3–11 years)	FP 2 puffs 220 μ g/puff BID added to other Tx; dose then reduced by 50% for another 24 weeks in responders	24–48		Mean alternate day OCS dose: 38 mg	Mean alternate day OCS dose after 3 months: 2.5 mg 6 patients (66%) discontinued OCS Significant improvements in mean per-patient asthma exacerbations ($P = .016$), ED visits (.016), hospitalizations ($P = .016$), school absences ($P = .004$) with no deterioration in asthma control

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Table 6 (continued)

Author, year	Design	Subjects, mean age, years (Range)	Treatments, dose	Duration (weeks)	Controllers other than indicated treatments at baseline	Baseline OCS mg/day (prednisone equivalent)	Outcomes
Vogelmeier et al, 2015 ¹⁰²	DBPC	n = 120 (18–65 years)	BID dosing: BUD 1000 µg by computer-controlled nebulizer (n = 80); placebo (n = 40)	18	Other ICS or ICS/LABA (continued during study)	BUD: 10.1 ± 7.1 mg; Placebo 10.4 ± 8.2 mg	%Subjects with ≥50% Reduction in OCS with clinical stability: BUD, 80%; Placebo, 62.5% (P = .04)

Abbreviations: BDP, beclomethasone dipropionate; BID, twice a day; BUD, budesonide, DBPC, double-blind, placebo-controlled; FP, fluticasone propionate; ICS, inhaled corticosteroid; LABA, long-acting beta₂-agonist; n, number of subjects; OCS, oral corticosteroid; QID, 4 times per day; TID, 3 times per day; SABA, short-acting beta₂-agonist; Sx, symptom(s).

puffs on 2 consecutive days).³³ The primary outcome measure was time to treatment failure, which was defined broadly as any of the following:

- Hospitalization or urgent care visit for asthma
- Systemic corticosteroids for asthma
- Increase in controller therapy
- A decrease in prebronchodilator FEV₁ ≥ 20% below randomization
- ≥2 consecutive days with a 35% decrease in morning PEF from baseline
- >10 puffs of rescue SABA over 2 consecutive days
- Withdrawal by subject choice or physician judgment

None of the step-down strategies was clearly superior. Approximately one third of subjects did not maintain control over the 48 weeks of treatment, with no significant between-group differences. The most common reasons for failure were using OCS (51% overall), >20% decrease in prebronchodilator FEV₁ (27%), and hospitalization or other urgent care visit (30%). Prebronchodilator FEV₁ decreased by -0.13 L in the FP monotherapy group compared to either combination group (FP 250 µg/salmeterol 50 µg, *P* < .001; FP 100 µg/salmeterol 50 µg, *P* < .027).³³

Patients Using ICS and Tiotropium

Some patients at step 4 may be using tiotropium in place of LABA as an addition to ICS monotherapy, particularly patients who are sensitive to the adverse effects (eg, palpitations, tremulousness) of LABA.^{1,3,4,73} Other patients may be using tiotropium and medium-dose ICS/LABA to provide added clinical benefit without an increase in ICS dose.^{3,4,74,75} For patients whose condition is well controlled on tiotropium with ICS/LABA, a first step in the step-down strategy would be to discontinue the long-acting muscarinic agent (LAMA) and maintain the patient on the ICS/LABA. For patients whose conditions are well controlled on tiotropium and ICS, discontinuing the LAMA is the recommended first step. Given the limited data available, consideration may be given to reducing the dose of ICS before discontinuing tiotropium, particularly for patients who may be sensitive to the adverse effects of ICS. Careful monitoring is needed.

Summary and Recommendations

Most patients whose conditions are well controlled at step 4 are using moderate to high doses of ICS, often with another medication (eg, LABA, tiotropium). The currently available data do not provide high-quality evidence to support a strong recommendation for stepping down treatment from step 4 all the way to step 3 appropriate for all patients. Although most patients who entered step-down protocols in clinical trials managed to maintain control at a lower dose, particularly those in studies of ICS/LABA combination, there are caveats to applying the outcomes to real-world scenarios. These patients at step 4 therapy—despite having achieved a level of control over time—have struggled with moderate to severe disease, so monitoring their asthma status is critical, as is having a clear action plan for when to step up treatment and how to do that. For some patients who become symptomatic during peak allergen or virus seasons, an imposed seasonal step-up might be considered, but further data are needed. Immunotherapy may be helpful in further reducing the dose of ICS for patients with allergic asthma. Caution is warranted in patients who are exacerbation-prone.¹⁴

Again, stepping down ICS/LABA combination therapy is limited to some extent by the available products. Is a 50% decrease in ICS/LABA dose too steep a reduction for the patient? If so, a multiple-step strategy using lesser dose increments, such as described previously, might have more success. There is some flexibility in the

Table 7
Studies Reporting Reduction in Chronic Oral Corticosteroid (OCS) Use with Biologic Treatments

Author, year	Design	Subjects Mean age, years (Range)	Tx, Dose of biologic	Duration (weeks)	Baseline medication	Baseline OCS mg/day (prednisone equivalent)	Outcomes
Omalizumab							
Milgrom et al, 1999 ¹¹⁶	DBPC	n = 35 (11–50 years)	OMAL IV: 5.8 µg/kg/ng IgE antibody/mL (n = 9), 2.5 µg/kg/ng IgE antibody/mL (n = 14); Placebo (n = 12)	20	≥400 µg BDP/day	Median: 10 mg (2.5–40 mg)	%Subjects with ≥50% decrease in OCS from BL: High-dose, 78% (P = .04); Low-dose, 57% (P = .23); Placebo, 33%
Molimard et al, 2010 ¹¹⁷	Prospective (no control group)	n = 166 (46.1 ± 13.9 years)	SC dosing table	~24	ICS/LABA >95%	19.0 ± 16.3 mg	Mean reduction in daily OCS: 7.1 ± 12.3 Reduction in exacerbations: 3.9 ± 8.2
Siergiejko et al, 2011 ¹¹⁸	R, OL	n = 82 (12–75 years)	OMAL (n = 59), SC dosing table; No OMAL (n = 23)	32	>1000µg BDP/d + LABA	OMAL, 13.1 ± 9.2 mg; No OMAL, 12.8 ± 10.7 mg	%Reduction OCS from BL: OMAL, 45.0%; No OMAL, 18.3% (P = .002)
Lafeuille et al, 2012 ¹¹⁹	Retrospective Administrative claims data: 1 year pre- and 1 year post- OMAL	n = 644 (≥12 years; 8 = <12 years)	SC dosing table	52	High-dose ICS/LABA	All used some in prior 12 mo	%Subjects discontinued OCS: 53.3%
Schumann et al, 2012 ¹²⁰	Prospective (no control group)	n = 195 (6–68 years)	SC dosing table	26	GINA Step 4 care	n = 112 subjects treated with OCS at baseline (57.4%)	64 subjects (42.9 %) had a 49.2% reduction in frequency of OCS use
Brodie et al, 2012 ¹²¹	Prospective (no control group)	n = 34 (5–16 years)	SC dosing table	16	GINA Step 5 care	Median, 20 mg (2.5–50 mg)	Significant reduction to median of 5 mg/d (range, 0–40 mg/day) with significant improvements in mini AQLQ, ACT (all ages) and FEV ₁ (<12 years old)
Braunstaahl et al, 2013 ¹²²	Observational registry of OMAL users	n = 263 (≥12 years)	SC dosing table	52	ICS 1675 ± 947 µg BDP/d (equivalent)	15.5 ± 14.0 mg	Final OCS (12 months): 7.7 ± 10.9 mg/day; 57.1% of subjects reduced or stopped OCS at 198.5 ± 114.3 days
Chen et al, 2016 ¹²³	Retrospective database of OMAL users	n = 1585 (1.3 ± 17.2 years)	Not reported	>16	ICS/LABA (99.4%) LAMA (17.1%)	146 (92.4%) on C-OCS	91 subjects (57.1%) on C-OCS (P < .001); significant reduction in exacerbations
Mepolizumab							
Bel et al, 2014 ¹²⁴	DBPC Eosinophilic asthma (≥300 cells/mm ³ before screening or ≥150 cells/mm ³ at screening)	n = 135 (16–74 years)	100 mg SC every 4 weeks	20	High-dose ICS + 2 nd controller	Prior 6 mo, 5–35 mg/day; 47%–49% ≥5 years	Reduction in OCS: OR, 2.4 (95% CI, 1.3–4.6); Median % reduction, 50% vs 0 % (P = .005); 32% relative reduction in exacerbations (P = .04); ACQ significantly improved (P = .004)
Benralizumab							
Nair et al, 2017 ¹²⁵	DBPC	n = 220 Adults	30 mg SC every 4 weeks × 3 then either every 4 weeks or every 8 weeks; Placebo	28	ICS (250–5000 µg) + LM (33%–40%)	Median, 10 mg (7.5–40 mg) 6 months	Median dose reduction of 75% with both BENR regimens vs 25% with placebo (P < .001 for both); vs placebo, longer time to first asthma exacerbation (P < .001); improved ACQ (P < .001) and AQLQ (P = .004)
Dupilumab							

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Table 7 (continued)

Author, year	Design	Subjects Mean age, years (Range)	Tx, Dose of biologic	Duration (weeks)	Baseline medication	Baseline OCS mg/day (prednisone equivalent)	Outcomes
Rabe et al, 2018 ¹¹⁴	DBPC	n = 210 (≥12 years)	300 mg SC every 2 weeks; Placebo	24	High-dose ICS + 2 controllers ≥3 months	11.3 ± 6.1 mg ≥6 months for 1.7 ± 3.5 years	% OCS dose reduction: DUPIL, 70.1%; Placebo, 41.9% ($P < .001$) %Subjects with ≥50% OCS dose reduction: DUPIL, 80%; Placebo, 50%; Exacerbations decreased by 59% with DUPIL (95% CI, 37–74), and FEV ₁ increased by 0.22 L (95% CI, 0.09–0.34) vs placebo

Abbreviations: ACO, Asthma Control Questionnaire; ACT, Asthma Control Test; AQOLQ, Asthma Quality of Life Questionnaire; BDP, beclomethasone dipropionate; BENR, benralizumab; CI, confidence interval; DBPC, double-blind placebo-controlled; DUPIL, dupilumab; FEV₁, forced expiratory volume in 1 second; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; IV, intravenous; LABA, long-acting beta₂-agonist; LAMA, long-acting muscarinic agent; LM, leukotriene modifier; n, number of subjects; OCS, oral corticosteroid(s); OL, open-label; OMAL, omalizumab; OR, Odds Ratio; SC, subcutaneous; TX, treatment(s).

products (Table 3), and data suggest that patients well controlled on moderate or high doses of one ICS/LABA can be stepped down to a lower dose of that ICS/LABA or to a different combination product with no difference in efficacy.^{14,71,76} Nonetheless, decreasing the dose reduction to an increment of 10% or 20% is not possible with the currently available single inhalers.

With regard to stepping down from step 4 therapy, the authors note the following:

- At this level, carefully reviewing the patient's history to ensure that control has been maintained for at least 6 months and that there have been no exacerbations in the previous year are equally important.
- For patients using ICS/LABA, reduce the dose of ICS while maintaining LABA, recognizing that switching between products may be necessary to allow smaller steps in the titration process.
- For patients using tiotropium + ICS, titration might start with a lower dose of ICS while maintaining the tiotropium, followed by discontinuing tiotropium if control is maintained.
- For patients using tiotropium + ICS/LABA, the tiotropium may be discontinued and the patient maintained on the ICS/LABA.
- Control should be established and maintained between titration steps for at least 3 months and preferably longer.

Stepping Down from Step 5 Therapy

Stepping down therapy for patients being treated at the step 5 level should be approached with greater caution. These patients are at the most severe level of asthma and likely have experienced poor asthma control in the past.^{3,4,77–82} They may have failed initial treatments with ICS alone and even subsequent treatments with additional controller medications such as LABA, LAMA, and LM. Duration of control is a critical factor for these patients; many do not experience prolonged periods of stability. The provider should exercise more caution, but not rule out the possibility of step-down in properly selected patients. Control over a period of time—ideally, with no exacerbations—may present an opportunity for a step-down attempt. How long control should be maintained for these patients before stepping down is unclear. Although 3 months of asthma control is the generally used recommendation for when to consider stepping down at other severity levels,¹ patients with severe disease require longer periods of stability, and at this level the authors recommend at least 6 to 12 months of control with no exacerbations.

Before consideration of stepping down therapy, the patient should be assessed for adequate asthma control, adherence to appropriate step 5 treatments, adequacy of techniques with various inhaler devices, and previous allergic and seasonal trigger patterns. A careful timeline of previous step-up and corresponding responses to each step also may provide additional input when selecting which of multiple medications to step down.

Reducing the Burden of Chronic Oral Corticosteroids

Many patients at step 5 are treated with high-dose ICS/LABA plus other controller medications. Almost all of these patients use OCS to treat exacerbations; some require OCS on a chronic basis (C-OCS) as maintenance therapy.^{3,4,82–85} Recent epidemiologic studies convincingly document the increase in disease burden and costs associated with C-OCS use^{82–90} (Table 5). Several definitions are used to classify C-OCS use, including OCS dose (average cumulative mg/day/year) and courses (number/year). The studies show that OCS doses as low as 2.5 mg/day/year,⁸² ≥ 30-day supply/year,⁸⁴ 2-year cumulative dose ≥ 3.9 g,⁸⁶ or ≥ 4 courses/year^{82,85} are associated with increases in corticosteroid adverse effects, adverse comorbidities, health-care utilization, and cost. Equally important, C-OCS use

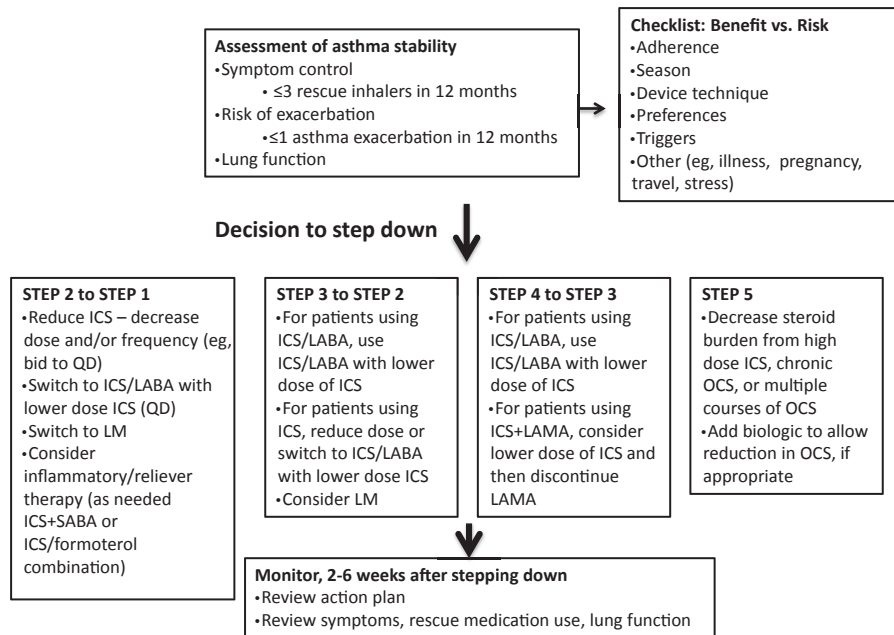


Figure 2. Recommendations for stepping down asthma therapy.⁶ Abbreviations: FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic agent; LM, leukotriene modifier; OCS, oral corticosteroid; QD, once-a-day; SABA, short-acting beta₂-agonist.

is an independent predictor for future C-OCS use.^{82,85} The data support a recommendation to titrate down the dose of OCS whenever possible, even in patients with severe and difficult-to-control asthma. More information about the burden imposed by C-OCS use is provided in eCommentary 2.

C-OCS Sparing with ICS Treatment

As detailed earlier, although addressing adherence to medication is important at all GINA step-care levels, it is paramount to objectively document medication adherence in patients at step 5. A systematic review of 10 small double-blind, placebo-controlled trials noted that a daily dose of prednisolone 7.5 to 10 mg/day appeared to be equivalent to moderate- to high-dose ICS, but at the expense of more adverse effects.⁹¹ Are patients requiring C-OCS using their medium- to high-dose ICS or ICS/LABA as prescribed? If not, the need for C-OCS may not be warranted. *Cochrane Systematic Reviews* have documented that the addition of ICS significantly reduced or led to the discontinuation of OCS.^{92–94} A dose-dependent OCS-sparing effect was not apparent for budesonide 1600 µg/day vs 800 µg/day or 400 µg/day, but was evident for lung function in severe asthma,⁹⁵ although this was based on only a few studies. A systematic review reported that ICS provided substantial OCS-sparing.⁹⁶ Many double-blind, placebo-controlled, or comparator-randomized studies have documented the efficacy and effectiveness of different types of ICS to reduce OCS^{97–104} (Table 6). In these studies, ICS was associated with discontinuation of OCS in 43% to 85% of severe asthma patients compared with placebo^{95–100} and with improvements in spirometry^{95–99} and disease burden, including exacerbations.^{99,101} A more recent study in adults with severe asthma continued on ICS or ICS/LABA reported that nebulized budesonide at 1 mg bid with a special computer-driven nebulizer led to a significant reduction in C-OCS dose compared with placebo.¹⁰² The benefits of ICS treatment in reducing the need for C-OCS were seen in adolescents and adults (Table 6) and also in children.⁹⁶

Tapering C-OCS

Tapering C-OCS is the next stage in the care of patients requiring step 5 medication, including OCS, despite optimal adherence to treatment and management of relevant comorbidities. Various anti-inflammatory drugs and immune suppressants have been

tried with either no or little benefit and some level of risk for new adverse effects from the therapies. *Cochrane Systematic Reviews* have extensively reported on generally small, randomized double-blind clinical trials of these interventions. Those yielding small and probably clinically unimportant reductions in C-OCS included methotrexate,¹⁰⁵ cyclosporin,¹⁰⁶ and gold.¹⁰⁷ Interventions with no benefit for C-OCS-sparing included troleandomycin,¹⁰⁸ macrolides,¹⁰⁹ chloroquine,¹¹⁰ and azathioprine.¹¹¹ With the recent FDA approval of effective and safe biologics for the treatment of severe asthma, clinicians and patients no longer need to experience the poor risk–benefit profiles of these anti-inflammatories and immune suppressants.

C-OCS Sparing with Biologics

Three classes of biologic therapies—those targeting anti-IgE (omalizumab),¹¹² anti-IL-5 (mepolizumab, reslizumab, benralizumab),¹¹³ and anti-IL-4/anti-IL-13 (dupilumab)¹¹⁴ pathways—are FDA-approved for the treatment of severe asthma. A paradigm shift in asthma control and the quality of lives of patients with severe asthma has been achieved with these biologics. *Cochrane systematic reviews* of randomized double-blind trials document their efficacy and safety in patients with moderate to severe asthma.^{112–114}

Establishing control (eTable 1) with the appropriate biologic agent is necessary before attempting to reduce the dose of OCS.¹¹⁵

Anti-IgE. Twenty-five trials of omalizumab in children, adolescents, and adults consistently showed, compared with placebo, 1) reduction of severe asthma exacerbations (OR, 0.55; 95% CI, 0.42–0.60) and hospitalizations (OR, 0.16; 95% CI, 0.06–0.42), and 2) discontinuation of ICS (OR, 2.50; 95% CI, 2.00–3.13) but not withdrawal for OCS therapy.¹¹¹ Significantly less serious adverse effects were observed with omalizumab compared with placebo (OR, 0.72; 95% CI, 0.57–91). Subgroup analyses showed that patients on C-OCS attained greater asthma control.¹¹² Only studies with subcutaneous administration of omalizumab were included in the *Cochrane* report. As noted in Table 7, the study by Milgrom and colleagues¹¹⁶ using intravenous omalizumab reported a significant reduction in the number of patients with a 50% reduction in C-OCS dose. Although the randomized double-blind data on the C-OCS-sparing

effect of omalizumab are modest, several open-label controlled trials have provided reasonable evidence supporting C-OCS-sparing potential for omalizumab^{117–123} (Table 7). A large long-term prospective randomized double-blind placebo-controlled trial of omalizumab in C-OCS step 5 patients is needed for definitive confirmation of these findings.

Anti-IL5 Therapies. Three anti-IL-5 medications are FDA-approved: mepolizumab and benralizumab for patients 12 years old or younger and reslizumab for adults. The Cochrane group reviewed 13 randomized double-blind placebo-controlled anti-IL-5 studies that included 6000 patients ages 12 years and older.¹¹³ Compared with placebo, anti-IL-5 therapies significantly reduced severe asthma exacerbations by approximately 50%, improved health-related quality of life, and evidenced a small (0.08–0.11 L) but significant improvement in FEV₁.¹¹³ All 3 showed markedly reduced blood eosinophil levels, with almost complete depletion by benralizumab. Greater benefit was seen at higher levels of blood eosinophils. No excess in serious adverse effects was observed with the anti-IL-5 therapies compared with placebo, although more discontinuations occurred with benralizumab.¹¹³

Table 7 includes 2 steroid-sparing double-blind placebo-controlled trials of the anti-IL-5 therapies, none of which were included in the Cochrane review. Treatment with mepolizumab produced a significant reduction in OCS (median reduction, 50% vs placebo, 0%; $P = .005$) and improvement in asthma control ($P = .004$) in 135 patients (16–74 years old) on step 5 care, using C-OCS, and with evidence for elevated blood eosinophils.¹²⁴ A trial of benralizumab in 220 adults on C-OCS and step 5 care reported a 75% median dose reduction in C-OCS compared with a 25% decrease with placebo ($P < .001$), while also demonstrating fewer asthma exacerbations ($P < .001$) and improved asthma control ($P < .001$).¹²⁵ An OCS-sparing study has not been reported for reslizumab.

IL-4/IL-13 Antagonism. Dupilumab, an IL-4/IL-13 antagonist, has recently obtained FDA approval as an add-on maintenance treatment for patients 12 years of age or older with moderate to severe asthma exhibiting an eosinophilic phenotype or with OCS-dependent asthma. In adolescents and adults on step 5 care and C-OCS, dupilumab was associated with a 71% OCS dose reduction vs 41.9% for placebo ($P < .001$), while also exhibiting significant reductions in asthma exacerbations and improved lung function.¹¹⁴

The data support the addition of omalizumab for properly selected children, adolescents, and adults, mepolizumab and dupilumab for adolescents and adults, and benralizumab for adults with C-OCS and step 5 care as OCS-sparing therapies. Studies are needed for reslizumab in all ages and benralizumab in adolescents as well as pediatric studies of all of the anti-IL-5 therapies.

In all of these studies, the reduction in OCS occurred concomitantly with improvements in exacerbation rates and asthma control measures.^{114,124,125} The patients were able to maintain control of their asthma despite the reduction in OCS. However, the current observations are based on single trials, and more studies are needed.

Stepping Down from Biologics

The questions of how long a patient should stay on a biologic and whether step-down is feasible have no clear answers. Limited data are available for omalizumab. The Evaluating Xolair Persistency of Response After Long-Term Therapy (XPORT) trial was a year-long prospective double-blind, placebo-controlled, randomized clinical trial of 152 patients who had been treated with omalizumab for more than 5 years and were randomized to continue or stop treatment.¹²⁶ Based on exacerbation rates, the data favored continuing omalizumab (OR, 0.44; 95% CI, 0.23–0.82). Data from other studies are mixed: some observational outcomes showed sustained control

of asthma after discontinuing omalizumab,^{117,127–129} although another did not,¹³⁰ and a randomized controlled trial evaluating correlations between outcomes and IgE changes reported that stopping omalizumab would likely worsen asthma control.¹³¹ More recently, a successful tapering protocol for omalizumab (treatment for ≥ 1.5 years) and OCS was reported in 35 mostly OCS-dependent (5 mg mean daily prednisone-equivalent dose) adults with severe allergic asthma.¹³² Omalizumab was tapered by half every 6 months if asthma stability was maintained and was increased to the previous dose if an OCS boost was necessary or spirometry worsened by less than 10%. Over a 12- to 30-month period, omalizumab was discontinued in 34% of patients, reduced successfully in 23%; 43% did not tolerate a reduction. Oral corticosteroids were discontinued in the subgroup that was able to stop omalizumab. Although the number of patients was small and larger studies are needed, the report provides justification to attempt tapering omalizumab after 1 year or more of treatment in adults with documented stable asthma.¹³²

Data are not currently available for the anti-IL-5 drugs or dupilumab. A clinical trial examining step-down from mepolizumab is expected to be completed in 2019.¹³³

Summary and Recommendations

Patients being treated with step 5 therapy are at the most severe level of asthma and likely have experienced poor asthma control in the past.^{3,4,77–82} Any step-down should be approached with greater caution. Almost all of these patients use OCS, frequently to treat exacerbations and some on a chronic basis (C-OCS) as maintenance therapy.^{3,4,82–85} Recent epidemiologic studies convincingly document the increase in disease burden and costs associated with C-OCS use.

A goal then is to taper OCS as possible, which may be attempted if asthma control has been stable for at least 6 to 12 months. Reducing OCS doses should be approached with caution, both to minimize the potential risk of asthma recurrence and to limit the risk of uncovering adrenal suppression. The GINA guidelines do not provide a recommendation for OCS tapering, nor are there agreed-on OCS tapering algorithms. Giving the absence of consensus on OCS tapering, one should review the several studies presented in Table 7. A representative approach was detailed in the mepolizumab OCS sparing study.¹²⁴ After successful tapering of OCS, consideration should be given to tapering high-dose ICS to lower doses, as described in the previous section (Stepping Down from Step 4 Therapy).

Biologic agents may help to restore asthma control, particularly in the risk domain (ie, exacerbations), and possibly may permit tapering of OCS. However, the evidence for discontinuing biologic agents once implemented is insufficient to make specific recommendations. The patients at step 5 are considered high-risk, and close monitoring is recommended both for tapering OCS and for decisions regarding stepping down biologics.

The authors suggest the following caveats when considering a possible decrease in step 5 therapy:

- First assure that the patient is truly at step 5 level care.
 - Objectively evaluate OCS and controller therapy use to determine adherence. Electronic medical record pharmacy dispensings and medical records from previous providers may be helpful. Do not rely solely on patient reports, which may be inaccurate and biased upward.
 - A trial of at least 3 months on high-dose ICS/LABA under direct supervision is essential to determine responsiveness to future control and risk.
 - Assess asthma control objectively with a validated control tool (eTable 2).

- Assess asthma risk objectively with documentation of exacerbations.
- Document the efficacy/effectiveness of moderate- to high-dose ICS and ICS/LABA to reduce OCS dependency.
- Consider a trial of an appropriate biologic agent after documenting continued OCS dependency despite adequate adherence and poor response to ICS/LABA (or to LM in those not tolerating LABA).
 - Duration of trial: minimum 4–6 months (if control is not documented)
 - Assess asthma control improvement with validated control tool (eTable 2), using clinically meaningful effect.
 - Assess risk by documenting the absence of exacerbations or a decreased rate of exacerbations compared with a similar prior time interval.
 - Attempt to taper OCS over 2–4 months.
 - Documented improvement with biologic should include:
 - Maintenance of asthma control
 - Reduced or no exacerbations
 - Decrease in dose of OCS
 - Duration of biologic treatment after improvement is documented:
 - Current data are insufficient to make a recommendation for the timing of biologic taper or discontinuation.

Discussion

Stepping down asthma therapy is an important component of managing patients with asthma, from the mildest end of the severity spectrum to the most difficult-to-treat patient. However, although current guidelines recommend stepping down therapy in a patient with stable asthma, the operational focus has been on how to step up treatment when asthma is inadequately controlled.^{1,2} This Yardstick provides recommendations for how to step-down therapy using guideline-based severity levels.

Several caveats should be kept in mind. First, all patients with persistent asthma should be treated with an anti-inflammatory medication, preferably an ICS. Even at the mildest end of the spectrum, no patient with persistent asthma should use reliever medication alone. For patients at this level of severity who are likely to be adherent, once-daily therapy with an anti-inflammatory agent is recommended; for patients not likely to be adherent with or who do not prefer daily treatment, an anti-inflammatory/reliever protocol may be better.

Second, all patients should be treated with the lowest dose of corticosteroid that maintains asthma control. For patients with mild persistent disease, this may be achieved as described—using once-daily therapy or anti-inflammatory/reliever protocols. However, for patients with severe asthma, a primary goal for stepping down is to limit the steroid burden, from chronic use of OCS, multiple courses of OCS, or regular use of high-dose ICS. Biologics may be helpful in appropriate patients. For patients with allergic asthma, immunotherapy may help further reduce the dose of ICS.

Third, the process of considering a step-down in management should include an individualized assessment of the potential for benefit compared with the potential for harm, which should be discussed with the patient. Patients (and families) should be involved in the decision-making process and permitted to express their values and preferences, prioritizing continued control by maintaining the current dose and not stepping down; or stepping down, which may pose a greater risk for loss of asthma control but offers the potential for reducing medication reliance and, possibly, simplifying treatment and decreasing costs. The impact of accurately assessing the patient's adherence to controller medications cannot be understated and requires an honest conversation between the patient and the health care provider. The patient may

have independently decided to step down, or even stop, their medication, and that is an important point for the conversation.¹³⁴

As described in this paper, no one way exists to accomplish a step-down in therapy. The choices available allow some individualization of how to step down based on the patient's starting level of severity, medical history, and medication considerations, including dose and frequency of administration. Stepping down should be considered a process and not simply a jump from guideline-recommended treatment at one severity level to that at the next lower severity level. Multiple steps may be necessary to optimally step down from one severity level to the next. A partial step-down may be appropriate. The strategies described are summarized in Figure 2. The data suggest stepping down using a gradual reduction of ICS dose (25%–50%), after which discontinuation of other added medications (LAMA, LM, LABA) might be considered.⁵ Stepping down or suspending LM in patients with aspirin-exacerbated respiratory disease may be qualitatively different compared with aspirin-tolerant patients with asthma, and should be approached more carefully from the standpoint of the potential for benefit compared with the potential for harm.^{30,135}

The likelihood of a successful step-down is encouraged by a longer period of stability (at least 6 months)¹⁴ and ensuring that the patient understands and agrees to the step-down process, along with careful monitoring and use of an action plan for the patient once step-down has been initiated.^{5,6} The time of year when initiating a step-down also may contribute to a successful outcome; for many patients with asthma, symptoms vary with season. Guidelines recommend avoiding stepping down during times when patients are at high risk for exacerbation such as during a patient's allergy season or during times of the year when viral upper respiratory tract infections are more likely (eg, the start of the school year).^{1,6,15,136}

Risk modeling to identify other markers of success (or failure) remains a goal. Potential predictors, including clinical and demographic characteristics (eg, disease duration^{61,137} age,⁶⁰ bronchial hyperresponsiveness,^{61,138} lung function,⁶¹ and biomarkers (eg, FeNO,^{57,61,139} serum eosinophils,^{56,58,59,82,129} sputum eosinophils,^{56,60,137,139,140} serum eotaxin¹⁴¹) have been proposed, but the data are inconclusive.

In summary, this is the first Yardstick presenting recommendations for stepping down asthma controller therapy according to guideline-based severity at all levels. A variety of options are available for patients with stable asthma who are, ideally, at low risk for future exacerbations. Although the recommendations are based on available data, the studies are limited and comparisons difficult because of differences in design, duration of treatment, definition of asthma control, and patient populations. Specific studies are needed that prospectively evaluate the recommendations included in this Yardstick, and long-term studies are needed to compare different step-down strategies over time. Monitoring step-down, evaluating adherence, and understanding shared decision-making from the patient perspective also require further definition. Some recommendations in this document may merit revision based on evidence forthcoming in future studies.

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Appendix

eCommentary 1. Methods

For the initial draft of the manuscript, the authors worked in teams to review the GINA 2018^{e1} guideline-based recommendations for stepping-down therapy along with appropriate data available in the literature: Dr. Bacharier and Dr. Lang, Stepping down from GINA Step 3; Dr. Murphy and Dr. Oppenheimer, Stepping down from GINA Step 4; Dr. Zeiger and Dr. Rank, Stepping down from GINA Step 5. The data were not weighted. Each team then developed a “best practice summary” for their step-down section according to the described approaches modified by the clinical expertise and commentary of the group. All authors reviewed and provided appropriate revisions to all drafts of the manuscript and gave written approval to the final document. It is anticipated that, like the guidelines, the Asthma Controller Step-down Yardstick will be updated on a regular basis.

eCommentary 2. Burden of chronic oral corticosteroid use

Reported studies generally agree that C-OCS use is associated with significant increases in the following comorbidities and corticosteroid-associated adverse effects: infections (notably, pneumonias and herpes zoster), gastrointestinal illnesses (particularly peptic diseases), bone (fractures, osteopenia, osteoporosis, low bone density), cardiac (cardiovascular, hypertension), metabolic (obesity, diabetes type 2, hypercholesterolemia), ocular (cataracts), psychiatric (affective disorders including anxiety, depression, sleep disorders), and chronic kidney disease^{e2–e10} (Table 5 in text). Patients requiring C-OCS also may have increases in total health care utilization.^{e3,e6,e7} Females on C-OCS appear to be at increased risk for comorbidities and cost.^{e6,e8} Specific types of comorbidities may occur at younger or older ages.^{e6} Many of these effects are dose-dependent, increasing with higher C-OCS doses or courses.^{e2,e3,e5,e6,e9} In addition, asthma disease burden is greater with C-OCS: patients show greater risk (more asthma exacerbations, ED visits, hospitalizations), more

impairment, reduced quality of life, lower spirometry, and increased need for rescue medication.^{e2,e5,e10} In other words, C-OCS use represents a negative spiral of risk and impairment and has been shown to be an independent predictor for future C-OCS use.^{e2,e5} One would anticipate that qualitatively similar C-OCS adverse comorbidities would occur in children younger than 12 years of age, although data are needed.^{e5}

Two meta-analyses of studies from 2007 to 2016 that examined the adverse effects and costs associated with long-term systemic corticosteroid exposure in patients with mainly diseases other than asthma reported increased costs and adverse effects,^{e11,e12} similar to those reported in Table 5 (in text) in patients with asthma. A questionnaire-based study of 367 older adult patients using C-OCS, 44% with asthma, and 734 controls without C-OCS indicated that C-OCS significantly increased costs associated with 1) fractures of the vertebrae, hip, ribs, and sternum, which were OCS dose-related, 2) cataracts, 3) muscle weakness, 4) bruising, 5) oral candidiasis, and 6) loss of teeth.^{e13} A greater risk of hip and vertebrae fractures was reported in a large British administrative data study for adults using an average OCS dose of at least 7.5 mg/day prednisone-equivalent.^{e14} The risk increased with daily dose, age, and female sex, but not type of disease. More recently, a population-based cohort study investigating the association of C-OCS to osteonecrosis in patients with chronic inflammatory diseases, including asthma, found no evidence for an increased occurrence of osteonecrosis in children on C-OCS or in adults on low-dose OCS (<7 mg/day or maximum dose <30 mg/day).^{e15}

A large Danish birth cohort from 1995–2003 ($n = \sim 6$ million) observed that for children with asthma, any OCS use was associated with an increase by adolescence in the risk for psychoses, but not schizophrenic spectrum disorders, as compared with children who did not use OCS.^{e16} Corticosteroid-induced adrenal suppression in children and adults on ICS was found to be associated with variations in the platelet-derived growth factor gene in a genome-wide association discovery and validation study, results that may be extrapolated to C-OCS use as well.^{e17}

eTable 1Assessing Asthma Control by Impairment and Risk^{e18}

A. Children ages 12 years and older (and adults)			
Components of control	Classification of asthma control		
	Well controlled	Not well controlled	Very poorly controlled
Impairment			
Symptoms	≤2 days/week	>2 days/week	Throughout the day
Nighttime awakenings	≤2×/month	1-3×/week	≥4×/week
Interference with normal activities	None	Some limitation	Extremely limited
Using SABA for symptoms (not prevention of EIB)	≤2 days/week	>2 days/week	Several times/day
FEV ₁ or PEF	>80% predicted/personal best	60%-80% predicted/personal best	<60% predicted/personal best
Validated questionnaires:			
ACT	≥20	16-19	≤15
ACQ	≤0.75	≥1.5	N/A
ATAQ	0	1-2	3-4
Risk			
Exacerbations requiring OCS	≤1/year	≥2/year	
Progressive loss of lung function	Long-term follow-up required		
Treatment-related adverse effects	May vary from none to troublesome/worrisome. Intensity does not correlate with level of control, but should be considered in overall assessment of risk		
B. Children ages 5-11 years			
Components of control	Classification of asthma control		
	Well controlled	Not well controlled	Very poorly controlled
Impairment			
Symptoms	≤2 days/week and not >1×/day on those days	>2 days/week or multiple times on ≤2 days/week	Throughout the day
Nighttime awakenings	≤1× /month	≥2× /month	≥2×/week
Interference with normal activities	None	Some limitation	Extremely limited
Using SABA for symptoms (not prevention of EIB)	≤2 days/week	>2 days/week	Several times/day
FEV ₁ or PEF	>80% predicted/personal best	60%-80% predicted/personal best	<60% predicted/personal best
FEV ₁ /FVC	>80%	75%-80%	<75%
Validated questionnaires: cACT	≥20	13-19	≤12
Risk			
Exacerbations requiring OCS	≤1/year	≥2/year	
Progressive loss of lung function	Long-term follow-up required		
Treatment-related adverse effects	May vary from none to troublesome/worrisome. Intensity does not correlate with level of control, but should be considered in overall assessment of risk.		
C. Children ages 0-4 years old			
Components of control	Classification of asthma control		
	Well controlled	Not well controlled	Very poorly controlled
Impairment			
Symptoms	≤2 days/week	>2 days/week	Throughout the day
Nighttime awakenings	≤1×/month	≥1×/month	≥1×/week
Interference with normal activities	None	Some limitation	Extremely limited
Using SABA for symptoms (not prevention of EIB)	≤2 days/week	>2 days/week	Several times/day
Validated questionnaires: TRACK	Score of 80-100	A change in the TRACK score ≥10 points indicates a clinically meaningful change in respiratory or asthma control; for children with symptoms consistent with asthma, this should alert the health care provider to review the child's asthma treatment plan	
Risk			
Exacerbations requiring OCS	≤1/year	2-3/year	>3/year
Treatment-related adverse effects	May vary from none to troublesome/worrisome. Intensity does not correlate with level of control, but should be considered in overall assessment of risk.		

Abbreviations: ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; ATAQ, Asthma Therapy Assessment Questionnaire for Children and Adolescents; c-ACT, Childhood Asthma Control Test; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; OCS, oral corticosteroid; PEF, peak expiratory flow rate; SABA, short-acting beta₂-agonist; TRACK, Test for Respiratory and Asthma Control in Kids.

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eTable 2
Validated Asthma Control Questionnaires

Questionnaire	Description	Included in questionnaire					Other comments
		Symptom frequency	Rescue therapy use	Sleep disturbance	Activity limitation	Exacerbations	
Asthma Control Test (ACT) ^{e20,e21}	Ages: ≥ 12 years old 5 questions answered monthly	X	X	X	X	No	- Overall self-rating of control included; each item scored from 1-5 - Maximum score = 25 - Score <19 suggests asthma not controlled - MID = 3 - Survey license request required for use
Childhood ACT (cACT) ^{e22,e23}	Ages: 4-11 years old 7 questions answered monthly (by parent and/or child)	X	No	X	X	No	- Overall parent/child rating of control included: 4 questions to child, maximum score for each = 3; 3 questions for parent, maximum score for each = 5 - Combined maximum score = 27 - Score <19 suggests asthma not controlled; score <12 suggests asthma poorly controlled - MID = 2
Pediatric Asthma Therapy Assessment Questionnaire for Children and Adolescents (pATAQ) ^{e24}	Ages: 5-17 years old 7 questions answered monthly (by parent/caregiver)	X	X	X	X	No	- Overall parent rating of control domain scored 0, no asthma control problems, to 7, very high rates of asthma-related health care utilization - No MID
Asthma Control Questionnaire (ACQ) ^{e25-e27} and in children cACQ ^{e28}	Ages: 6-16 years old (and adults) 7 questions, including FEV ₁ , completed weekly. Shorter versions with symptoms only (5 questions) or symptoms + rescue medication (6 questions) or symptoms + FEV ₁ (6 questions) validated in patients ≥6 years old Trained interviewer required for children 6-10 years old	X	X	X	X	No	- Items measured on scale of 0-6; score is averaged - Score ≥ 1.5 suggests asthma is uncontrolled; score < 0.75 suggests asthma is well controlled. - MID = 0.5 - Permission needed from author to use^{e41,e42}
Test for Respiratory and Asthma Control in Kids (TRACK) ^{e29,e30}	Ages: ≤ 5 years old 5 questions answered by parents/caregivers: 3 on monthly symptoms, 1 on 3-month rescue medication use, 1 on exacerbations in past year	X	X	X	X	X	- Each item scored from 0-20 - Maximum score = 100 - Score < 80 suggests possible poor control of child's breathing problems - Change in score ≥ 10 points suggests the need to reevaluate the child's treatment - MID = 10
Composite Asthma Severity Index ^{e31,e32}	Ages: 6-17 years old 5 domains: daytime symptoms and albuterol use (last 2 weeks); nights with symptoms and albuterol use (last 2 weeks); lung function (current); controller treatment (current); exacerbations (last 2 months)	X	X	X	No	X	- Maximum score = 20 - A change ≥ 1 point suggests a change in asthma severity; for defining asthma risk levels, a CASI score of ≤ 3 identifies mild asthma (though an increase in the CASI score represents increased severity above and below the cutoff point) - Predominantly a research tool - CASI is free to use, and sample forms, calculator, and other resources are publicly available at www.asthmaseverity.org.

Abbreviations: FEV₁, forced expiratory volume in 1 second; MID, minimal important difference.
(reprinted with permission from Chipps et al, 2018^{e19})

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