

Clinical reviews in allergy and immunology

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Approaches to stepping up and stepping down care in asthmatic patients

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The variability in symptom control is a challenging feature of asthma that necessitates careful monitoring and the need to step up and step down individualized therapeutic regimens over time. This stepwise concept in asthma therapy can be considered in at least 3 contexts. For lack of control that is persistent over long periods of time, an increase in the overall medication or a step-up long-term strategy is indicated. A second approach, the step-up short-term strategy, can be used during a temporary loss of acceptable control, such as at the onset of a viral respiratory tract illness. In these cases a step-up in therapy is usually terminated in 3 to 10 days once asthma control has been satisfactorily achieved. Finally, for treating symptoms related to the variability of asthma on a day-to-day basis, inhaled corticosteroids used concomitantly with a β -agonist have been evaluated, although this treatment is not currently approved in the United States. We will term this particular intervention a step-up intermittent strategy. Here we summarize the existing data regarding these 3 approaches to

step up care and step down management, as well as to identify areas where more comparative studies are necessary to provide further guidance to clinicians regarding proper step-up and step-down strategies in the care of asthma. (J Allergy Clin Immunol 2011;■■■:■■■-■■■.)

Key words: Asthma, step-up, step-down, stepwise, guidelines, severity, control, step-up intermittent, step-up short-term, step-up long-term

Asthma is characterized by chronic airway inflammation, variable airflow obstruction, airway hyperresponsiveness, and recurrent symptoms.¹ The variability in symptom control is a particularly challenging feature of asthma that necessitates careful monitoring and the need to step up and step down individualized therapeutic regimens over time. To provide guidance to clinicians regarding proper step-up and step-down strategies, both national (National Asthma Education and Prevention Program that has published 3 Expert Panel Reports [EPRs]) and international (Global Initiative for Asthma [GINA]) panels have continued to convene to review evidence and provide structured recommendations based on both the published literature and expert opinion when scientific and clinical data have been lacking.¹⁻⁴

Crucial for the appropriate management of asthma are consistent measures to assess disease progression and response to therapy. As described in the EPR-3 report, the effective assessment and monitoring of asthmatic patients are closely linked to the concepts of severity, control, and responsiveness to treatment.⁵ *Asthma severity* is defined as the intrinsic intensity of the disease process. Severity is measured most easily and directly in a patient not receiving long-term controller therapy. *Asthma control* is defined as the degree to which the manifestations of asthma (symptoms, functional impairments, and risks of untoward events) are minimized and the goals of therapy are met. *Responsiveness* to therapy is the ease with which asthma control is achieved by therapy. Both asthma severity and control are evaluated by using the domains of current impairment and future risk. *Impairment* is the frequency and intensity of symptoms and functional limitations the patient is experiencing or has recently experienced. *Risk* is the likelihood of asthma exacerbations, progressive decrease in lung function (or, for children, reduced lung growth), and/or risk of adverse effects from medication.

In terms of the assessment of current impairment, both the frequency and intensity of symptoms are measured. This can be assessed by further delineating asthma symptoms, such as the frequency of nighttime awakenings, the need for a short-acting β -agonist (SABA) for the quick relief of symptoms, the number of work or school days missed, the effect on activities of daily

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Abbreviations used

AMD:	Adjustable maintenance dosing
EPR:	Expert Panel Report
FDA:	US Food and Drug Administration
GINA:	Global Initiative for Asthma
GOAL:	Gaining Optimal Asthma Control
ICS:	Inhaled corticosteroid
LABA:	Long-acting β -agonist
LTRA:	Leukotriene receptor antagonist
mAPI:	Modified asthma predictive index
NIH:	National Institutes of Health
PEF:	Peak expiratory flow
SABA:	Short-acting β -agonist
SLT:	Step-up long-term
SST:	Step-up short-term
SUI:	Step-up intermittent

living, and quality-of-life assessments. Validated questionnaires, such as the Asthma Control Test,⁶ the Childhood Asthma Control Test,⁷ the Asthma Control Questionnaire,⁸ the Asthma Therapy Assessment Questionnaire control index,⁹ and others have been used more frequently in recent years to help standardize the quantification of impairment. In addition to patient-reported symptoms, spirometry as a means to measure lung function can aid in classifying both severity and control.¹⁰

The EPR-3 emphasizes the importance of periodic assessments at 1- to 6-month intervals to assess asthma control. The goal of asthma therapy is to maintain long-term control by using the smallest amount of medication possible. Responsiveness to treatment is variable between patients, and follow-up assessments are critical to determine whether the goals of therapy are being met.⁵ It is during these interval assessments that one must determine whether the goals of therapy are being met and decide whether the dose, number of medications, and/or frequency of administration should be increased, if necessary, and decreased when possible.

CHOOSING THE INITIAL STEP OF CARE

In patients naive to asthma therapy, the initial step in choosing a therapeutic regimen is based on defining asthma severity (Fig 1). Patients with intermittent asthma are placed in the first of the 6 steps of the EPR-3 guideline-defined stepwise approach for managing asthma: as-needed use of SABAs (Fig 2). Should SABA use exceed 2 days per week, this would increase the patient's severity level to persistent asthma, and a step-up would be recommended. Two exceptions to this guideline are exercised-induced bronchospasm and viral respiratory tract infections. For virus-induced exacerbations occurring more than every 6 weeks, a step-up (step 2) in therapy is recommended.⁵

For patients whose symptoms are not controlled by step 1 intermittent SABA therapy (eg, daytime symptoms >2 days per week, nighttime symptoms >2 days per month, worsening lung function, and >2 exacerbation per year), step 2 care should also be initiated. Inhaled corticosteroids (ICSs) are the preferred treatment for step 2 therapy across ages.

Once the initial step of care is chosen, the patient should be re-evaluated periodically to determine whether his or her asthma control is satisfactory. If the current step of care is not controlling the patient's asthma based on the criteria defined in the EPR-3

guidelines (Fig 3), a step-up in care is initiated. Conversely, if the step of care has produced adequate control for prolonged periods of time, consideration should be given to step-down therapy based on the EPR-3 guideline recommendations.⁵

STRATEGIES FOR STEP-UP AND STEP-DOWN MANAGEMENT

The concept of step-up and step-down management in asthma therapy can be considered in at least 3 contexts (Fig 4). First, if lack of control is persistent over long periods of time (eg, 2-3 weeks or longer), an increase in the overall medication regimen will be prescribed by moving up 1 or 2 steps, as defined in the EPR-3 or GINA asthma guideline recommendations.^{4,5} We will term this particular intervention the step-up long-term (SLT) strategy. This step-up in overall therapy is usually continued for 3 to 6 months to evaluate the ability and consistency of the new regimen to maintain adequate asthma control. At this point, consideration could be given to stepping down 1 absolute level with the stipulation that re-evaluation should occur within the next 1 to 2 months to determine the consistency of control that this step-down regimen is able to maintain over time. A second approach to step-up therapy might occur in relationship to an anticipated brief loss of control (days), such as at the onset of a viral respiratory tract illness¹¹ or as a consequence of an acute short-term exposure (eg, a furred pet) that has been known to induce a temporary loss of acceptable asthma control.¹² In most cases this will entail a step-up in therapy consisting of more frequent short-acting β -agonist (SABA) use and, potentially, an increase from baseline in the dose of ICS aimed at preventing a more significant exacerbation requiring oral corticosteroid treatment. This step-up in therapy is usually terminated in 3 to 10 days once asthma control has been satisfactorily achieved; at this point, a step-down to the baseline medication regimen is instituted. For the purposes of this review, we will term this particular intervention the step-up short-term (SST) strategy. Finally, for treating symptoms related to the variability of asthma on a day-to-day basis, an ICS used concomitantly with a SABA or a long-acting β -agonist (LABA) has been evaluated. Although this type of therapy has been studied in clinical trials and approved for use in many parts of the world, it is currently not approved in the United States. We will term this particular intervention the step-up intermittent (SUI) strategy. Interestingly, this approach has been used in both step-up (using LABAs and SABAs)¹³ and step-down (using SABA)^{14,15} treatment approaches.

SLT STRATEGY

The SLT strategy was initially evaluated in moving from step 2 to step 3 care in adult patients whose asthma was not well controlled with low doses of ICSs. Studies by both Greening et al¹⁶ and Woolcock et al¹⁷ using the SLT approach demonstrated that, in patients who symptoms are not well controlled on a low dose of ICSs, the addition of a LABA was superior to increasing the dose of ICS for many outcome measures in the impairment domain. These observations were subsequently extended to the risk domain in the Formoterol and Corticosteroid Establishing Therapy study.¹⁸ This study evaluated the effect of adding a LABA to a fixed ICS dose, quadrupling the dose of ICS, or both on reducing asthma exacerbations. For 1 year, patients were treated twice daily with 100 μ g of budesonide, 100 μ g of budesonide and 12 μ g

Components of Severity		Classification of Asthma Severity (Age ≥ 12 years)			
		Intermittent	P e r s i s t e n t		
			Mild	Moderate	Severe
Impairment	symptoms	≤ 2 days/week	> 2 days/week but not daily	daily	throughout the day
	nighttime awakenings	≤ 2x /month	3-4x/month	>1x/week but not nightly	7x/week
	SABA use for symptom control	≤ 2 days/week	> 2 days/week but not >1x/day	daily	several times per day
	interference with normal activity	none	minor limitation	some limitation	extremely limited
	lung function	Normal FEV ₁ between exacerbations FEV ₁ >80% predicted FEV ₁ /FVC normal	FEV ₁ ≥80% predicted FEV ₁ /FVC normal	FEV ₁ >60% but <80% predicted FEV ₁ /FVC reduced 5%	FEV ₁ <60% predicted FEV ₁ /FVC reduced >5%
Risk	exacerbations requiring oral systemic corticosteroids	0-1/year	≥2/year		
		Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. Relative annual risk of exacerbations may be related to FEV ₁ .			
Recommended Step for Initiating Treatment		Step 1	Step 2	Step 3	Step 4 or 5
		consider short course of oral corticosteroids			
In 2-6 weeks, evaluate level of control that is achieved and adjust therapy accordingly					

FIG 1. Classification of asthma severity. Adapted from the EPR-3.⁵ FVC, Forced vital capacity.

of formoterol, 400 µg of budesonide, or 400 µg of budesonide and 12 µg of formoterol. With the addition of a LABA to a lower dose of ICS, severe exacerbations were reduced by 26%, and mild exacerbations were reduced by 40% when compared with lower-dose ICSs alone. The higher dose of ICS alone reduced the rates of severe exacerbations by 49% and mild exacerbations by 37%. When a LABA was added to the higher dose of ICS, severe exacerbations were reduced by 63%, and mild exacerbations were reduced by 62%. Both lung function and asthma symptoms improved with both higher ICS doses and formoterol, although the greatest improvements were achieved with formoterol.

The issue of which SLT intervention leads to better overall asthma control when choosing between more ICS versus adding a LABA was comprehensively studied by Bateman et al¹⁹ in the Gaining Optimal Asthma Control (GOAL) study. This randomized, double-blind, parallel-group study assessed the ability of predefined stepwise adjustments of fluticasone/salmeterol or fluticasone alone to achieve 2 predefined measures of asthma control. The definitions of control included composite measures of peak expiratory flow (PEF), rescue medication use, daytime and nighttime symptoms, exacerbations, emergency department visits, and other adverse events based on the GINA or National Institutes of Health (NIH) guidelines.⁴ Unlike previous studies of controller therapy that focused on improvements with fixed doses of medications, the GOAL study allowed for dose escalation in a stepwise approach to achieve more comprehensive and sustained control. Phase I of the study was the dose-escalation phase. During this time, treatment was stepped up every 12 weeks until asthma was totally controlled or until the medication reached 500 µg of fluticasone twice daily or 500/50 µg of fluticasone/salmeterol twice daily. Once asthma control was totally achieved or after 12 weeks of maximal medication dosing, the patients were advanced to phase II, the constant phase. During this double-

blind treatment period, patients continued to take the same dose of controller medication for 1 year. Of note, in an effort to determine whether there were incremental effects over time of continuing to take these medications, there was no step-down treatment plan during this phase. Although the majority of patients achieved well-controlled or totally controlled asthma in this study, approximately 9% of patients in the fluticasone-only group and 5% of patients in the fluticasone/salmeterol group did not achieve well-controlled asthma in phase I or phase II, requiring escalation to the maximum treatment phase or oral corticosteroids and 500/50 µg of fluticasone/salmeterol. Nevertheless, the GOAL study provided strong evidence that patients with uncontrolled asthma from a varied range of severity were able to achieve and sustain guideline-defined control. It also demonstrated that stepping up therapy to achieve guideline-defined control, even in patients who did not achieve the most stringent definitions of “total control,” still resulted in significant improvements in health status and rates of exacerbation. Bateman et al¹⁹ did emphasize that many risks of sustained treatment might take years to become clinically significant, and further research into step-down therapy once control was achieved was indicated. Regardless, the possibility of achieving guideline-based total control through medication escalation provided solid evidence for a stepwise approach to asthma management.

A recent study completed by the Childhood Asthma Research and Education network has provided evidence to guide SLT in children whose symptoms are uncontrolled on low doses of ICSs and who require step 3 care. The Best Add-on Therapy Giving Effective Responses trial was a double-blind, 3-treatment, crossover trial in children aged 6 to 17 years with asthma uncontrolled by 100 µg of twice-daily fluticasone.²⁰ The ICS step-up consisted of 250 µg of fluticasone twice daily, the LABA step-up was 100/50 µg of fluticasone/salmeterol twice

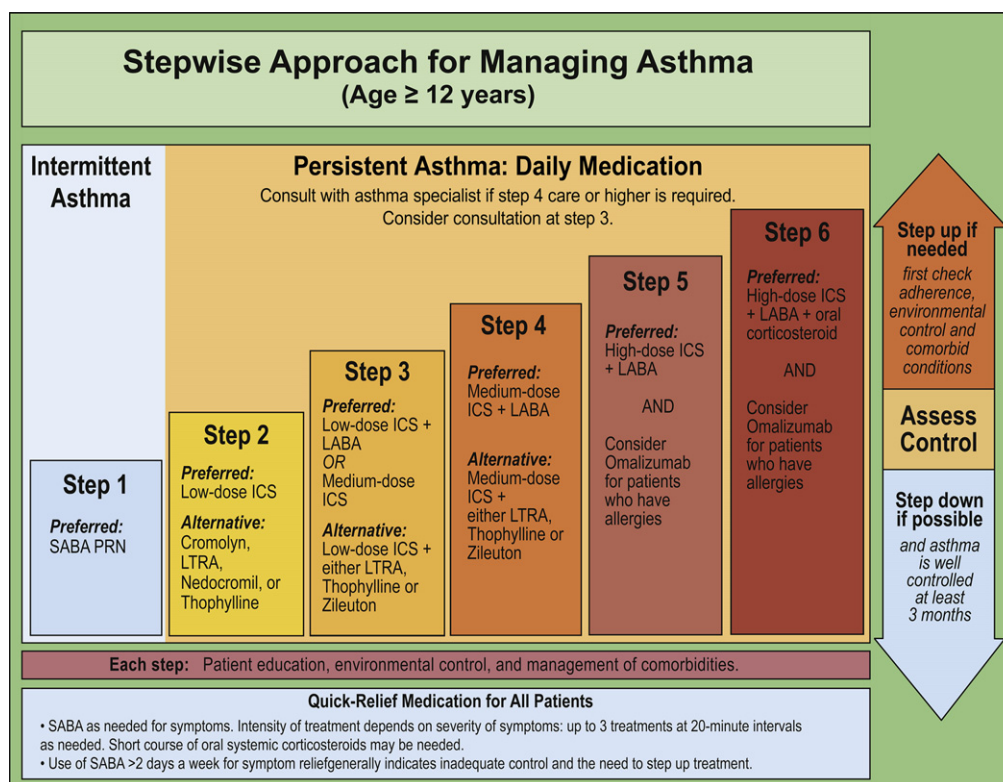


FIG 2. Stepwise approach for managing asthma. Initial step in therapy determined by asthma severity. Adjustment in therapy must take into account control and other patient characteristics such as risk. Adapted from the EPR-3.⁵ PRN, As needed.

daily, and the leukotriene receptor antagonist (LTRA) step-up was 100 µg of fluticasone twice daily plus 5 or 10 mg of montelukast daily. The primary outcome was the differential response to each therapy based on a composite outcome of 3 measures in both the risk (exacerbations requiring oral prednisone) and impairment (the number of asthma control days and FEV₁) domains of asthma control. Remarkably, a differential response to therapy was demonstrable in 98% of the patients, and there were no differences in response patterns based on age. Overall, LABA step-up led to the greatest likelihood of best response; however, some children had better responses with one of the other 2 therapies. This study emphasized the importance of regularly monitoring each child's response to medication and providing appropriate adjustment of therapy. Moreover, the findings also demonstrate that in the event that a child is not responding to a specific step 3 therapy, rather than escalate to step 4 care, alternative step 3 treatments should be considered.

Safety concerns regarding the chronic use of LABAs²¹ have provided impetus for evaluating additional options in moving from step 2 to step 3 care. In this regard the efficacy of an inhaled anticholinergic medication (tiotropium bromide) in comparison with either doubling doses of ICSs or the addition of a LABA was recently examined. Peters et al²² hypothesized that the addition of tiotropium bromide in patients with inadequately controlled asthma would be more effective than doubling the dose of ICS and that the addition of the long-acting anticholinergic would not be inferior to the addition of a LABA. Compared with doubling glucocorticoid dosing, the use of tiotropium resulted in a greater improvement in morning and evening PEF, pre-bronchodilator FEV₁, and daily symptom scores and a greater

proportion of asthma control days. Tiotropium also was not inferior compared with the addition of salmeterol in all outcomes assessed. Although the duration of treatment was limited to 14 weeks in this study and long-term safety issues or rates of exacerbations could not be taken into account fully, the results suggest that another efficacious step-up treatment option when moving from step 2 to step 3 care might be the addition of a long-acting cholinergic antagonist.

Step-up and step-down strategies with various biomarkers believed to be relevant to asthma pathophysiology have also been evaluated. Biomarkers evaluated have included methacholine airway hyperresponsiveness,²³ sputum eosinophil counts,²⁴ and exhaled nitric oxide levels.^{25,26} Although these approaches have shown promise in reducing exacerbations, improving asthma control, or both, measurements of airway hyperresponsiveness and sputum eosinophil counts, although performed in many subspecialty practices and research centers, are not routinely available in most primary care practices. Exhaled nitric oxide levels are currently being measured in many outpatient settings, although their overall contribution to patient management, cost-effectiveness, and specificity to asthma are still not definitively established.^{27,28}

Strategies for choosing SLT to steps 4 through 6 have not been evaluated as rigorously. However, recent work using interventions with mAbs directed at either the allergic (eg, omalizumab) or immunoinflammatory (mepolizumab) response have provided new insights regarding which patients should be considered for step-up treatment involving these treatments. Humbert et al²⁹ examined the effect of anti-IgE mAb (omalizumab) in patients whose severe allergic asthma was inadequately controlled despite

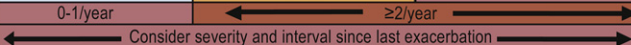
Components of Control			Classification of Asthma Control (Age ≥ 12 years)		
			Well Controlled	Not Well Controlled	Very Poorly Controlled
Impairment	symptoms	≤ 2 days/week	> 2 days/week but not daily	throughout the day	
	nighttime awakenings	≤ 2x /month	3-4x/month	7x/week	
	interference with normal activity	none	minor limitation	extremely limited	
	SABA use for symptom control	≤ 2 days/week	> 2 days/week	several times per day	
	FEV ₁ or peak flow	>80% predicted / personal best	60-80% predicted / personal best	<60% predicted / personal best	
	Validated questionnaires				
		ATAQ	0	1-2	1-2
		ACQ	≤ 0.75	≥ 1.5	N/A
	ACT	≥ 20	16-19	≤ 15	
Risk	exacerbations requiring oral systemic corticosteroids	0-1/year			
	Progressive loss of function	Evaluation requires long-term followup care			
	Treatment-related adverse effects	Medication side effects can vary in intensity from none to very troublesome and worrisome. The level of intensity does not correlate to specific levels of control but should be considered in the overall assessment of risk.			
Recommended Action for Treatment		Maintain current step	Step up 1 step and reevaluate in 2-6 weeks	Consider short course of oral systemic corticosteroids, Step up 1-2 steps, and reevaluate in 2 weeks.	
		Regular followups every 1-6 months to maintain control	For side effects, consider alternative treatment options.	For side effects, consider alternative treatment options.	
		Consider step down if well controlled for atleast 3 months			

FIG 3. Classification of asthma control. Adapted from the EPR-3.⁵ ACQ, Asthma Control Questionnaire; ACT; Asthma Control Test; ATAQ, Asthma Treatment Assessment Questionnaire; N/A, not applicable.

STEP-UP LONG-TERM (SLT)	STEP-UP SHORT-TERM (SST)	STEP-UP INTERMITTENT (SUI)
increase in therapy for uncontrolled asthma (weeks)	increase in therapy for brief loss of control (days)	increase in therapy for variable symptoms (day-to-day)
persistent loss of control	brief loss of control (upper respiratory tract infections, pet exposure)	mild symptoms
step-down therapy when control achieved after 3-6 months	step-down therapy when control achieved after 3-10 days	intermittent use

FIG 4. Stepwise management of asthma in 3 strategies. For persistent loss of control over long periods of time, SLT is indicated for an increase in the overall medication regimen of 1 to 2 steps per EPR-3 or GINA guidelines. SST occurs with a brief loss of control, usually requiring more frequent SABA dosing, an increase in baseline ICSSs, or both. SUI refers to intermittent use of combination ICS/LABA or ICS/SABA for the day-to-day treatment of variable asthma symptoms.

high-dose ICS and LABA therapy with a reduced lung function and a recent history of asthma exacerbations. In this randomized, double-blind, parallel-group, placebo-controlled trial of 419 patients, patients were started on omalizumab or placebo for 28

weeks. After adjustment for baseline exacerbation history, there was a 26% reduction in clinically significant exacerbation rates in the omalizumab group compared with the placebo group. Omalizumab also improved morning PEF, asthma symptoms scores, and asthma-related quality of life. Additionally, there were no significant side effects associated with the omalizumab group, with the most common adverse event being a local injection-site reaction. Therefore Humbert et al concluded that omalizumab should be considered a step-up option in patients with poorly controlled asthma despite high-dose ICS and LABA therapy.

A recent study by Busse et al³⁰ comparing the addition of omalizumab versus placebo to guideline-based care in patients aged 6 to 20 years has also demonstrated its effectiveness in preventing asthma exacerbations across steps of asthma severity, suggesting that omalizumab might be considered for SLT in patients with frequent exacerbations. Currently, omalizumab is US Food and Drug Administration (FDA) approved for patients aged 12 years and above with moderate-to-severe allergic asthma.⁵

The efficacy of an anti-IL-5 mAb (mepolizumab), which is known to decrease eosinophil recruitment and survival, has been recently studied as well. In an early study of anti-IL-5 in human subjects with mild asthma, anti-IL-5 treatment decreased sputum and blood eosinophil counts after inhaled allergen challenge but had no effect on either the late-phase response or the postallergen

increase in airway responsiveness to histamine.³¹ In another randomized, double-blind, placebo-controlled trial, patients with severe asthma and persistent eosinophilia were given anti-IL-5 mAb for 1 year. The treatment group had significantly less exacerbations and lower eosinophil counts but no significant changes from baseline in symptoms, FEV₁, bronchodilator use, or airway hyperresponsiveness.³² Similar findings were seen in a study of mepolizumab in patients with persistent eosinophilia and corticosteroid-dependent asthma. In addition to a significant decrease in the number of exacerbations, the treatment group also had a lower corticosteroid burden.³³

Although omalizumab and mepolizumab have shown efficacy for SLT in patients with more severe asthma, comparison studies are needed to provide the clinician with evidence to guide individualized approaches to choosing SLT regimens at steps 4 to 6 of asthma care.

SST STRATEGY

A number of clinical trials have evaluated variations on the SST strategy for both step-up and step-down approaches to therapy. Noting the common practice of doubling ICSs for the onset of exacerbations, Fitzgerald et al³⁴ evaluated this approach for loss of control not responding to rescue SABAs alone in a double-blind, randomized, controlled trial of 290 patients. Patients in the maintenance dose group received a maintenance dose of budesonide (100, 200, or 400 µg twice daily) plus placebo inhaler to be used twice daily within 48 hours of the onset of an exacerbation. Patients in the double-dose group received the same maintenance ICS dose plus an additional inhaler to be used twice daily for exacerbations that doubled the patient's ICS dose. The primary outcome measure was failure to regain control after having symptoms of an impending exacerbation. The number of subjects with asthma exacerbations was not significantly different between the maintenance dose group (n = 52) and the double-dose group (n = 46), and treatment failure was equivalent in both study groups. Thus doubling the dose of ICS was not effective in the management of impending asthma exacerbations.

Osborne et al³⁵ investigated whether quadrupling the dose of ICS would be an effective option for attenuating impending exacerbations. In addition to their usual asthma treatment, patients were randomized to placebo or a quadrupled ICS dose in an inhaler used with a decrease in PEF. The primary outcome, oral corticosteroid-requiring exacerbation, was less frequent in the treatment group, but this was not statistically significant. However, in patients who were adherent to the study protocol (ie, administered their study inhaler), exacerbations were significantly reduced by more than 50%. Collectively, these data indicate that increased doses of ICSs for SST might be effective in reducing oral corticosteroid exacerbations if the dose is high enough and the medication is started early enough.

Boushey et al³⁶ approached SST using another trial design. They recruited patients with EPR guideline-defined mild persistent asthma whose symptoms were well controlled with low doses of ICS and then randomized them to one of 3 groups: low-dose ICS (200 µg twice daily), an LTRA (20 mg of zafirlukast), or placebo. All 3 groups, when an *a priori* definition of lack of control was achieved, activated a symptom-based action plan, which consisted of open-label budesonide (800 µg twice daily) for 10 days or prednisone (0.5 mg/kg of body weight per day) for 5 days if their asthma symptoms worsened. Thus, although labeled as the

placebo group, these subjects received intermittent therapy that can be classified as an SST strategy. The 3 treatments produced similar increases in morning PEF and similar rates of asthma exacerbations. Compared with intermittent therapy or daily zafirlukast therapy, daily budesonide therapy produced greater improvements in prebronchodilator FEV₁, bronchial reactivity, percentages of eosinophils in sputum, exhaled nitric oxide levels, scores for asthma control, and the number of symptom-free days but not in postbronchodilator FEV₁ or quality of life (*P* = .18). Daily zafirlukast therapy did not differ significantly from intermittent treatment in any outcome measured. On the basis of these results, the authors concluded that it might be possible to treat mild persistent asthma with short intermittent courses of inhaled or oral corticosteroids taken when symptoms worsen.

Another SST strategy, termed adjustable maintenance dosing (AMD), using combination therapy with an ICS and a LABA, has been studied by a number of groups. Fitzgerald et al¹³ compared fixed dosing with fluticasone/salmeterol (250/50 µg twice daily) versus AMD with budesonide/formoterol (400/12 µg twice daily). After a run-in period with each of these dosing strategies, patients in the budesonide/formoterol arm subsequently halved their dose and were then permitted to step up or step down numbers of puffs per day, as indicated by the presence or absence of nocturnal awakenings caused by asthma, frequency of rescue medication use, and changes in morning PEF. After 48 weeks of therapy, stable dosing of 250/50 µg of fluticasone/salmeterol twice daily resulted in significantly greater increases in symptom-free days, days free of rescue medication, and morning PEF, as well as almost halving the exacerbation rate, compared with AMD with formoterol/budesonide. The authors concluded that there is a minimum daily amount of maintenance therapy necessary to prevent exacerbations in adults with persistent asthma.

In contrast, using similar combinations of ICSs plus LABAs, Aalbers et al³⁷ found that AMD with budesonide/formoterol provided more effective asthma control by reducing exacerbations and reliever medication use compared with fixed-dose fluticasone/salmeterol. Ind et al³⁸ used a single combination product (formoterol/budesonide) to compare the degree of asthma control that AMD could achieve and maintain versus a fixed-dose strategy. In both groups symptom control was maintained or improved in 85% to 86% of patients, and 94% experienced no treatment failures. The authors concluded that AMD with budesonide/formoterol in a single inhaler provides effective asthma control at reduced medication doses. Similar results favoring AMD strategies have been generated by other research groups as well.³⁹

Finally, in preschool children intermittent therapy (SST) with ICSs or LTRAs for episodic disease was evaluated by Bacharier et al⁴⁰ in the Acute Intermittent Management Strategies study. Preschool-aged children were randomized to either take 1 mg of budesonide twice daily, 4 mg of montelukast daily, or placebo for 7 days at the first sign of a respiratory tract illness. The primary outcome was episode-free days, with a secondary outcome of symptom scores and oral corticosteroid use during illness. Among the 3 treatment groups, there was no significant difference in episode-free days, oral corticosteroid use, linear growth, health care use, or quality of life. There were more significant differences in symptoms in both the LTRA and ICS groups compared with the placebo group in children with a positive modified asthma predictive index (mAPI) score⁴¹ or prior oral corticosteroid use. The findings suggested that episodic use of high-dose

ICSs or LTRAs in children with intermittent asthma can decrease symptom burden during acute respiratory tract infections and most prominently in those with a positive mAPI score (and future risk for asthma) or previous use of corticosteroids (propensity for greater illness severity).

SUI STRATEGY

Because of the rapid onset of bronchodilation seen after administration of the LABA formoterol, various research groups have evaluated whether patients receiving combination therapy with formoterol/budesonide could use this medication not only for daily maintenance therapy but also for the intermittent treatment of symptoms for which albuterol would normally be administered (SUI). The rationale for this approach was that if this were shown to be therapeutic, patients would only need to possess 1 inhaler both for maintenance and reliever therapy. Moreover, the additional ICS that the patient would receive intermittently might further reduce the risk for exacerbations.

The STAY study was a multicenter clinical trial involving 2760 patients with asthma aged 4 to 80 years (FEV₁ 60% to 100% of predicted value).⁴² The patients were randomized to one of 3 treatment arms: either 0.4 mg of terbutaline as a SABA with 80/4.5 μ g of budesonide/formoterol twice a day (budesonide/formoterol plus SABA); 320 μ g of budesonide twice a day (budesonide plus a SABA); or 80/4.5 μ g of budesonide/formoterol twice a day with 80/4.5 μ g as needed (budesonide/formoterol maintenance plus relief). Budesonide/formoterol maintenance plus relief prolonged the time to the first severe exacerbation, resulting in a 45% to 47% lower exacerbation risk compared with the other 2 treatment options. Budesonide/formoterol maintenance plus relief also prolonged the time to the first, second, and third exacerbations requiring medical intervention, reduced severe exacerbation rates, and improved symptoms, awakenings, and lung function compared with both fixed-dosing regimens.

Despite these efficacy data, in the United States concern regarding potential safety issues for LABAs has dampened enthusiasm by the FDA to approve combination therapy for this type of SUI strategy.⁴³ If clinical trials specifically addressing these safety concerns can be successfully conducted, because of the large sample size needed to properly evaluate the outcomes of concern, it is possible that this step-up strategy might be re-evaluated and ultimately approved in the United States if no safety concerns can be demonstrated.⁴⁴

These potential concerns related to the safety of LABA administration have prompted alternative approaches to SUI. Two recent studies, one performed in adults by Papi et al¹⁴ and one in children by Martinez et al,¹⁵ have taken the novel approach of stepping down therapy in patients with asthma symptoms well controlled on low doses of ICSs (step 2 care) and using a SABA (albuterol) plus a dose of ICS each time the patient feels a need for albuterol rescue. Thus in one of the trial arms patients have the option of using intermittent step-up therapy when required for symptom control and, when doing so, receive not only a bronchodilator but also an anti-inflammatory medication.

In the adult study patients with mild asthma whose symptoms were controlled with 250 μ g of beclomethasone twice daily were randomly assigned to receive one of 4 inhaled treatments for 6 months: placebo twice daily plus 250 μ g of beclomethasone and albuterol in a single inhaler as needed (as-needed combination therapy); placebo twice daily plus albuterol as needed (as-needed

albuterol therapy); 250 μ g of beclomethasone twice daily and albuterol as needed (regular beclomethasone therapy); or 250 μ g of beclomethasone and albuterol in a single inhaler twice daily plus albuterol as needed (regular combination therapy). Remarkably, the number of exacerbations during the 6-month treatment was significantly lower in the as-needed combination therapy group (SUI) than in the as-needed albuterol therapy group but were not significantly different from those in the groups receiving regular beclomethasone therapy or regular combination therapy. Furthermore, the cumulative dose of inhaled beclomethasone was lower in the as-needed combination therapy group (SUI) than in the groups receiving regular beclomethasone therapy or regular combination therapy.¹⁴

The trial design of the pediatric study was similar, but the ICS and albuterol were both in separate inhalers (as opposed to the adult study in which both the ICS and albuterol were in a single inhaler). In this 44-week trial 288 children and adolescents aged 5 to 18 years with mild persistent asthma were assigned to one of 4 parallel treatment groups. The daily ICS group received 40 μ g of beclomethasone dipropionate twice daily and albuterol as a rescue medication. The rescue ICS (SUI) group received no daily controller and used 40 μ g of beclomethasone and albuterol as rescue medication. The combined group received both beclomethasone twice daily with albuterol and beclomethasone as a rescue. The placebo group received no daily controller and used albuterol alone as a rescue. The study's primary outcome was time to first exacerbation. Although the frequency of exacerbation was 49% in the placebo group, the frequency of exacerbation was 28% in the daily ICS group, 31% in the combined group, and 35% in the rescue ICS group. Linear growth was less in patients in the daily and combined ICS groups but not in the rescue group when compared with the placebo group. With exacerbation frequencies significantly less than the placebo group and comparable with those of the other treatment groups, patients in the rescue ICS group (SUI) received only 15% to 25% of the daily ICS that those in the combined and daily ICS groups received. Martinez et al¹⁵ concluded that in children with mild-to-persistent asthma, rather than a complete discontinuation of daily ICS therapy altogether, the use of ICS as a rescue medication might be an alternative step-down strategy. Thus intermittent step-up with ICS plus albuterol might be an option for children and adults whose asthma is on the border between step 1 and step 2 care.

STEP-DOWN

Because the goal of asthma therapy is to maintain long-term control by using the smallest amount of medication possible, EPR-3 guidelines recommend consideration of stepping down therapy if asthma remains well controlled for at least 3 months to reach a minimum effective dose.⁵ Although the Papi et al¹⁴ and Martinez et al¹⁵ studies in both adults and children provide novel approaches of stepping down therapy to intermittent dosing with SABAs and ICSs concomitantly, research comparing other step-down strategies at various levels of asthma severity is clearly needed across all age groups. Indeed, recently, the FDA proposed stepping down off LABAs in patients whose symptoms are well controlled with LABA plus ICS combination therapy (step 3 to step 2 care).²¹ However, 3 separate studies found that stepping off LABAs after the establishment of acceptable asthma control resulted in the patient's asthma symptoms becoming less well

controlled.⁴⁵⁻⁴⁷ Although confirmatory studies are needed, these initial results do not support the FDA's proposed recommendation that the step-down be withdrawal of LABAs.

CONCLUSION

The stepwise approach to asthma management must be considered in multiple contexts because loss of asthma control has variable presentations. Although we have summarized much of the existing literature using 3 different forms of step-up strategies (Fig 4), it is likely that other approaches will be found to be useful clinically as well. It is important to emphasize, however, that the most important factor in the successful use of a stepwise approach to asthma management that will achieve the greatest degree of control with the least amount of medication possible is scheduled follow-up care rather than crisis management alone.

What do we know?

SLT

- ICSs are the preferred step 2 therapy across all age groups.
- Stepwise-based medication escalation can lead to guideline-based total asthma control.
- In step-up of long-term care in children older than 5 years and adults from step 2 to step 3, the addition of a LABA is more likely to improve control compared with increased doses ($2\times$ - $2.5\times$) of an ICS.
- Tiotropium bromide might be a potential alternative to LABAs in adults.

SST

- Short-term increased doses of ICSs ($4\times$ baseline) might be effective in reducing exacerbations.
- Although not approved for use in the United States, the AMD of ICSs/LABAs provides effective asthma control in decreasing SABA use and exacerbation frequency.
- In preschool-aged children, short-term step-up of ICS or LTRA use decreases symptom burden in patients with acute respiratory tract infections in those with a positive mAPI score or a history of oral corticosteroid use.

SUI

- Concomitant use of an ICS plus a LABA or SABA might be effective for treatment of the day-to-day symptoms of asthma.

Step down

- In patients with well-controlled mild persistent asthma, rescue ICS plus SABA therapy is superior to SABA alone for step-down.
- Step-down from step 3 care with ICS/LABA to ICS alone results in asthma symptoms being less well controlled.

What is still unknown?

SLT

- Evidence to guide step 4 to 6 therapies in children older than 5 years and adults
- Evidence to guide step 2 to 6 therapies in children younger than 5 years
- Long-term efficacy and safety profile of tiotropium bromide used in step 3 care in adults
- Efficacy and safety of tiotropium bromide in children

SST

- Evidence to guide appropriate short-term step-up treatment in children younger than 5 years
- Safety and efficacy of an intermittent high-dose ICS added to a daily ICS in children younger than 12 years

SUI

- Role of a rescue ICS plus SABA as add-on therapy at step 3 and later

Step down

- Comparative studies of step-down therapy across all age groups and levels of severity
- Further confirmatory studies to guide stepping down from the LABA component of ICS/LABA combination therapy

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