Ann Allergy Asthma Immunol 113 (2014) 143–159

Contents lists available at ScienceDirect

Practice Parameter

Management of acute loss of asthma control in the yellow zone: a practice parameter

Chitra Dinakar, MD; John Oppenheimer, MD; Jay Portnoy, MD; Leonard B. Bacharier, MD; James Li, MD; Carolyn M. Kercsmar, MD; David Bernstein, MD; Joann Blessing-Moore, MD; David Khan, MD; David Lang, MD; Richard Nicklas, MD; Christopher Randolph, MD; Diane Schuller, MD; Sheldon Spector, MD; Stephen A. Tilles, MD; and Dana Wallace, MD

Chief Editors: Chitra Dinakar, MD; John Oppenheimer, MD; Jay Portnoy, MD

Members of the Joint Task Force on Practice Parameters: David Bernstein, MD; Joann Blessing-Moore, MD; David Khan, MD; David Lang, MD; Richard Nicklas, MD; John Oppenheimer, MD; Jay Portnoy, MD; Christopher Randolph, MD; Diane Schuller, MD; Sheldon Spector, MD; Stephen A. Tilles, MD; Dana Wallace, MD

Practice Parameter Workgroup: Chitra Dinakar, MD; John Oppenheimer, MD; Jay Portnoy, MD; Leonard Bacharier, MD; James Li, MD; Carolyn Kercsmar, MD

This parameter was developed by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma and Immunology; the American College of Allergy, Asthma and Immunology; and the Joint Council of Allergy, Asthma and Immunology.

Reprints: Joint Council of Allergy, Asthma and Immunology, 50 N Brockway Street, #304, Palatine, IL 60067.

Disclaimer: The American Academy of Allergy, Asthma and Immunology (AAAAI) and the American College of Allergy, Asthma and Immunology (ACAAI) have jointly accepted responsibility for establishing "Management of Acute Loss of Asthma Control in the Yellow Zone: A Practice Parameter." This is a complete and comprehensive document at the current time. The medical environment is a changing environment, and not all recommendations will be appropriate for all patients. Any person seeking to apply or consult this practice parameter is expected to use independent medical judgment in the context of individual clinical circumstances or seek out the supervision of a qualified clinician. The ACAAI, the AAAAI, and the Joint Council of Allergy, Asthma and Immunology (JCAAI) disclaim any legal liability associated with use of this practice parameter with respect to treatment of any individual. Because this document incorporated the efforts of many participants, no single individual, including those who served on the Joint Task Force, is authorized to provide an official AAAAI or ACAAI interpretation of these practice parameters. Any request for information about or an interpretation of these practice parameters by the AAAAI or ACAAI should be directed to the Executive Offices of the AAAAI, the ACAAI, and the JCAAI. These parameters are not designed for use by pharmaceutical companies in drug promotion.

Disclosures: The following is a summary of interests disclosed on Work Group Members' Conflict of Interest Disclosure Statements (not including information concerning family member interests). Completed Conflict of Interest Disclosure Statements are available upon request. Chitra Dinakar, MD (Chair) was on the speaker's bureau for Teva Pharmaceuticals, GlaxoSmithKline, and Aerocrine; John Oppenheimer, MD (Joint Task Force liaison) performed research and consulted for AstraZeneca, Glaxo, Merck, Sunovion, SrXA, Myelin, Sanofi Research, BI, Novartis, Medimmune, and Cephalon and was the Legal Defense Chair for ABAI and Annals of Allergy (Associate Editor); Leonard B. Bacharier, MD, had consulting arrangements with Aerocrine, Boeringher Ingelheim, DBV Technologies, GlaxoSmithKline, Genentech/Novartis, Merck, Teva, and Cephalon; has grants or grants pending with the National Heart, Lung, and Blood Institute/National Institutes of Health; and has received payment for lectures, including service on speakers' bureaus, from Aerocrine, AstraZeneca, Genentech, GlaxoSmithKline, Merck, Teva, and Schering-Plough; James Li, MD, owns stock in Novartis and Abbott; Jay Portnoy, MD, owns stock in Thermofisher and Mylan; Carolyn Kercsmar, MD, Chair, is DSMB for the GlaxoSmithKline-sponsored, Food and Drug Administration–mandated VESTRI pediatric study of the safety of long-acting β agonist plus inhaled corticosteroid in asthma management.

The Joint Task Force recognizes that experts in a field are likely to have interests that could come into conflict with development of a completely unbiased and objective practice parameter. To take advantage of that expertise, a process has been developed to prevent potential conflicts from influencing the final document in a negative way. At the workgroup level, members who have a potential conflict of interest either do not participate in discussions concerning topics related to the potential conflict or, if they do write a section on that topic, the workgroup completely rewrites it without their involvement to remove potential bias. In addition, the entire document is reviewed by the Joint Task Force and any apparent bias is removed at that level. Finally, the practice parameter is sent for review by invited reviewers and by anyone with an interest in the topic by posting the document on the Web sites of the ACAAI and the AAAAI.

The Joint Task Force has made a concerted effort to acknowledge all contributors to this parameter. If any contributors have been excluded inadvertently, the Task Force will ensure that appropriate recognition of such contributions is made subsequently.

Workgroup Members: **Workgroup Chair,** Chitra Dinakar, MD, Professor of Pediatrics, University of Missouri–Kansas City, Division of Allergy, Asthma and Immunology, Children's Mercy Hospitals, Kansas City, Missouri; **Joint Task Force Liaison,** John Oppenheimer, MD, Department of Internal Medicine, New Jersey Medical School, Pulmonary and Allergy Associates, Morristown, New Jersey; Jay M. Portnoy, MD, Director, Division of Allergy, Asthma & Immunology, The Children's Mercy Hospitals and Clinics, Professor of Pediatrics, University of Missouri–Kansas City School of Medicine, Kansas City, Missouri; Leonard B. Bacharier, MD, Professor of Pediatrics and Medicine, Clinical Director, Division of Pediatric Allergy, Immunology, & Pulmonary Medicine, Unit Co-Leader, Patient Oriented Research Unit, Washington University and St Louis Children's Hospital, St Louis, Missouri; James T. Li, MD, Professor of Medicine, Mayo Clinic, Rochester, Minnesota; Carolyn M. Kercsmar, MD, Director, Asthma Center, Professor of Pediatrics, Pulmonary Medicine, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; **Joint Task Force Members,** David I. Bernstein, MD, Professor of Clinical Medicine and Environmental Health, Division of Allergy/Immunology, University of Cincinnati College of Medicine, Cincinnati, Ohio; Joann Blessing-Moore, MD, Adjunct

http://dx.doi.org/10.1016/j.anai.2014.05.017
1081-1206/© 2014 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Classification of recommendations and evidence

There may frequently be a separation between the strength of recommendation and the quality of evidence.

Recommendation rating scale

Statement	Definition	Implication
Strong recommendation (StrRec)	A strong recommendation means the benefits of the recommended approach clearly exceed the harms (or that the harms clearly exceed the benefits in the case of a strong negative recommendation) and that the quality of the supporting evidence is excellent (Grade A or B)*. In some clearly identified circumstances, strong recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits strongly outweigh the harms.	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.
Recommendation (Rec)	A recommendation means the benefits exceed the harms (or that the harms clearly exceed the benefits in the case of a negative recommendation), but the quality of evidence is not as strong (Grade B or C)*. In some clearly identified circumstances, recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain and the anticipated benefits outweigh the harms.	Clinicians should also generally follow a recommendation but should remain alert to new information and sensitive to patient values and preferences.
Weak recommendation (Weak)	A weak recommendation means that either the quality of evidence that exists is suspect (Grade D)* or that well-done studies (Grade A, B, or C)* show little clear advantage to one approach versus another.	Clinicians should be flexible in their decision making regarding appropriate practice, although they may set bounds on alternatives; patient values and preferences should have a substantial influencing role.
No recommendation (NoRec)	No recommendation means there is a lack of pertinent evidence (Grade D)* and an unclear balance between benefits and harms.	Clinicians should feel little constraint in their decision making and be alert to new published evidence that clarifies the balance of benefit vs harm; patient preferences and values should have a substantial influencing role.

Category of evidence

- Ia Evidence from meta-analysis of randomized controlled trials
- Ib Evidence from at least 1 well-designed randomized controlled trial
- Ic Evidence from at least 1 randomized controlled trial that was not very well designed
- IIa Evidence from at least 1 controlled study without randomization
- IIb Evidence from at least 1 other type of quasi-experimental study
- IIc Evidence from 1 of the above that was not very well designed
- IIIa Evidence from well-designed nonexperimental descriptive studies, such as comparative studies
- IIIb Evidence from nonexperimental descriptive studies, such as comparative studies that were not very well designed
- IVa Evidence from expert committee reports or opinions or clinical experience of respected authorities or both

*Strength of evidence**

- A. Directly based on category I evidence that is well designed
- B. Directly based on category II evidence or recommendation from category I evidence that is not well designed
- C. Directly based on category III evidence or recommendation from category II evidence that is not well designed
- D. Directly based on category IV or recommendation from category III evidence that is not well designed
- LB Laboratory based
- NR Not rated

How this practice parameter was developed

The Joint Task Force on Practice Parameters

The Joint Task Force on Practice Parameters (JTF) is a 13-member task force consisting of 6 representatives assigned by the American

Clinical Faculty, Stanford University Medical Center, Department of Immunology, Palo Alto, California; David A. Khan, MD, Associate Professor of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas; David M. Lang, MD (methodologist), Head, Allergy/Immunology Section, Division of Medicine, Director, Allergy and Immunology Fellowship Training Program, Cleveland Clinic Foundation, Cleveland, Ohio; Richard A. Nicklas, MD, Clinical Professor of Medicine, George Washington Medical Center, Washington, DC; John Oppenheimer, MD, Department of Internal Medicine, New Jersey Medical School, Pulmonary and Allergy Associates, Morristown, New Jersey; Jay M. Portnoy, MD, Director, Division of Allergy, Asthma & Immunology, The Children's Mercy Hospitals & Clinics, Professor of Pediatrics, University of Missouri–Kansas City School of Medicine, Kansas City, Missouri; Christopher C. Randolph, Clinical Professor of Pediatrics, Yale-Affiliated Hospitals, Center for Allergy, Asthma, & Immunology, Waterbury, Connecticut; Diane E. Schuller, MD, Professor of Pediatrics, Pennsylvania State University Milton S. Hershey Medical College, Hershey, Pennsylvania; Sheldon L. Spector, MD, Clinical Professor of Medicine, UCLA School of Medicine, Los Angeles, California; Stephen A. Tilles, MD, Clinical Associate Professor of Medicine, University of Washington School of Medicine, Redmond, Washington; Dana Wallace MD, Assistant Clinical Professor of Medicine, Nova Southeastern University College of Osteopathic Medicine, Davie, Florida; **Invited Reviewers,** Donald Aaronson, MD, JD, Chicago, Illinois; Michael S. Blaiss, MD, Memphis, Tennessee; Michael B. Foggs, MD, Chicago, Illinois; Gary Rachelefsky, MD, Los Angeles, California; M. Razi Rafeeq, MD, Maumee, Ohio; Michael Schatz, MD, San Diego, California; Stuart Stoloff, MD, Reno, Nevada; Stan Szefler, MD, PharmD, Denver, Colorado.

Academy of Allergy, Asthma & Immunology; 6 by the American College of Allergy, Asthma & Immunology; and 1 by the Joint Council of Allergy and Immunology. This task force oversees the development of practice parameters; selects the workgroup chair(s); and reviews drafts of the parameters for accuracy, practicality, clarity, and broad utility of the recommendations for clinical practice.

The Yellow Zone Workgroup

The Yellow Zone Practice Parameter Workgroup was commissioned by the JTF to develop practice parameters that address management of acute loss of asthma control in the yellow zone. The chair (Chitra Dinakar, MD) invited workgroup members to participate in the parameter development who are considered experts in the field of asthma management. Workgroup members have been vetted for financial conflicts of interest by the JTF and their conflicts of interest have been listed in this document and are posted on the JTF Web site at http://www.allergyparameters.org. Where a potential conflict of interest was present, the potentially conflicted workgroup member was excluded from discussing relevant issues.

The charge to the workgroup was to use a systematic literature review, in conjunction with consensus expert opinion and workgroup-identified supplementary documents, to develop practice parameters that provide a comprehensive approach for identifying and managing acute loss of asthma control in the yellow zone based on the current state of the science.

Yellow zone practice parameter

The JTF developed Practice Parameters for the Diagnosis and Treatment of Asthma in 1995.[1] The first update was published in 1998.[2] Attaining Optimal Asthma Control: A Practice Parameter, published in 2005,[3] was the first focused update. This publication, Management of Acute Loss of Asthma Control in the Yellow Zone: Practice Parameter, represents the second focused update. In this practice parameter, the literature, relying on MEDLINE- and PubMed-referenced publications, was reviewed to determine an evidence-based guide to effectively recognize and treat acute loss of asthma control in the yellow zone. The recommendations in the practice parameter are intended to apply to the home setting only, not the office, emergency department (ED), or hospital settings.

Throughout this document, options are explored that include interventions that are not approved by the Food and Drug Administration (FDA). The authors do not recommend any one specific regimen but provide the current literature to allow the clinician to make choices from an evidence-based perspective.

Summary statements

Summary Statement 1: Asthma action plans typically follow a "traffic light" model with green, yellow, and red zones. Provide patients with an asthma action plan (written and/or electronic) that includes instructions for recognition of loss of control and activation of the yellow zone intervention plan. (Recommendation: B Evidence)

Summary Statement 2: Instruct patients to activate the yellow zone intervention plan when there is acute loss of asthma control in a setting outside a medical care facility, such as at home. The yellow zone (or zone of acute loss of control) is defined as:

- **An increase in asthma symptoms**
- **An increase in use of reliever medications**
- **A peak flow rate (PEFR) decrease of at least 15% OR a PEFR lower than 80% of personal best**
- **The presence or increase in nocturnal asthma symptoms. (Strong Recommendation: B Evidence)**

Summary Statement 3: Instruct patients to activate the yellow zone plan at the onset of an upper respiratory tract infection if this is a previously identified trigger. (Strong Recommendation: B Evidence)

Summary Statement 4: Instruct patients to escalate asthma therapy when they experience a loss of asthma control that puts them in the yellow zone. (Recommendation: B Evidence)

Summary Statement 5: Advise patients to use a short-acting β_2 agonist (SABA) for reliever use in the yellow zone at a dose of 2 to 4 puffs every 4 to 6 hours in addition to their escalated yellow zone treatment. If SABA use exceeds 12 puffs per day, advise patients to contact their provider for further guidance. (Recommendation: C Evidence).

Summary Statement 6: Advise patients currently treated with daily low-to-moderate dose inhaled corticosteroid (ICS) therapy to consider increasing the total ICS dose per 24 hours (ie, quadrupling) for managing loss of asthma control in the yellow zone. (Option: B Evidence)

Summary Statement 7: For children younger than 6 years with recurrent wheezing and risk factors for subsequent asthma (ie, positive modified asthma predictive index), consider initiating high-dose ICS or oral montelukast at the early signs of wheezing illnesses to decrease intensity of symptoms. (Option: B Evidence)

Summary Statement 8: For patients with mild to moderate asthma, consider recommending symptom-driven use of ICS with concomitant inhaled β agonist for control of yellow zone symptoms. (Option: B Evidence)

Executive summary

Asthma action plans have been recommended for all patients with asthma since the 1991 publication of the first National Heart, Lung, and Blood Institute (NHLBI) guidelines for the diagnosis and management of asthma. Establishment of a patient-provider partnership was a key component of the guidelines and the asthma action plan helped create this relationship by empowering patients to monitor their asthma status and take action when control deteriorated. The most recent iteration of the guidelines, the Expert Panel Report 3 (EPR3): Guidelines for the Diagnosis and Management of Asthma (EPR3), was developed by an expert panel commissioned by the National Asthma Education and Prevention Program Coordinating Committee, coordinated by the NHLBI of the National Institutes of Health. The EPR3 emphasized attainment of asthma control and recommended strategies to treat variations in symptoms that occur over a timeframe of months.

In addition to long-term variability of asthma control, most patients with asthma experience intermittent loss of control in response to exposure to acute triggers occurring over a shorter timeframe, such as hours to days. An asthma action plan is the logical tool to instruct patients on how to recognize and respond to such rapid changes in control that occur in a setting outside a supervised medical facility, such as the home. A typical asthma action plan includes written instructions regarding treatment recommendations in the green zone (asthma doing well), the yellow zone (asthma deterioration detected, intervention needed), and the red zone (asthma exacerbation requiring urgent treatment). Responding to the symptoms of acute loss of control in the yellow zone with effective interventions can help prevent deterioration to the red zone, necessitating use of systemic corticosteroids and/or urgent medical care.

The EPR3 recommends increasing administration of inhaled SABA (such as 2–6 puffs of albuterol) every 3 to 4 hours for 24 to 48 hours to treat home exacerbations of asthma. If there is insufficient improvement, it recommends adding a short course of oral systemic corticosteroids (Figure 5-4 of the EPR3). In other words, the

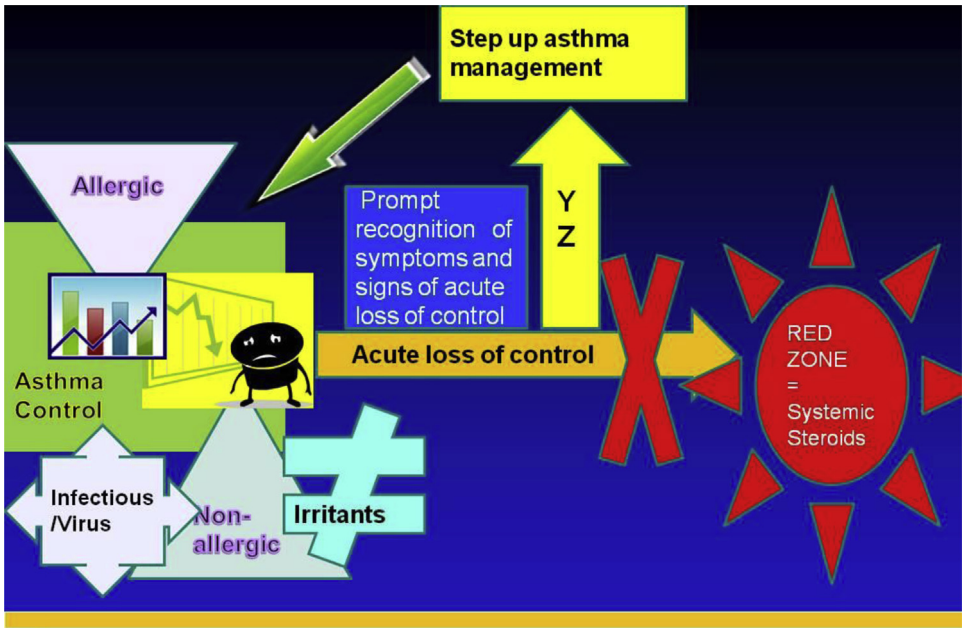

Figure 1. Yellow zone (YZ): the zone of acute loss of asthma control.

intervention recommended in the yellow zone by the EPR3 is to increase the frequency of reliever SABA therapy. Guidelines providing evidence-based therapeutic options to manage patients who experience short-term loss of control are therefore lacking, and this practice parameter was written with the intent of addressing the gap. This document attempts to define criteria that indicate acute loss of control into the yellow zone and reviews therapeutic maneuvers to regain asthma control and prevent further progression into the red zone. These recommendations are based on a meticulous and critical review of the medical literature, and in situations where data are lacking, options are presented.

The first recommendation in this practice parameter is that patients with asthma should be given a written and/or electronic asthma action plan. Although the format may vary, action plans most commonly follow the traffic light model. The green zone indicates asthma that is controlled, the yellow zone forewarns acute loss of control and an impending exacerbation, and the red zone indicates onset of a severe exacerbation requiring a course of systemic corticosteroids and contact with a health care provider. The action plans may be based on symptoms or on symptoms and peak expiratory flow (PEF), depending on the preference of the provider and the patient.

The second summary statement describes criteria for recognition of a yellow zone episode. In particular, patients should be advised to take action when they experience an increase in asthma symptoms, increased use of reliever medications, a decrease in their PEF (if they monitor it), or the onset of nocturnal symptoms. In addition, patients with a history of loss of control in response to respiratory tract infections (RTIs) are advised to take action.

The specific action to be taken is dependent on the severity of the episode and the individual response to previous episodes with those interventions. The ideal intervention should provide quick relief of symptoms, prevent progression to the red zone, be safe enough to initiate at home, be convenient and practical for self-administration, be portable so that it is always available, and be cost effective. Obviously, the perfect intervention does not exist; however, some potential interventions have been studied and are discussed below.

Potential interventions for yellow zone treatment include repetitive use of inhaled SABA administered through a metered dose inhaler or nebulizer, scheduled step-up of an ICS, and symptom-driven use of controller with reliever therapy, otherwise known as dynamic dosing or adjustable maintenance dosing (AMD). The regular scheduled use of SABA as the sole treatment for symptoms in the yellow zone is discouraged because it does not consistently prevent progression to the red zone and might increase the risk of progression.

Patients who are treated with daily ICS therapy can be advised to increase their total 24-hour ICS dose, for example, by 4-fold. Increase in the frequency of ICS administration over 24 hours also may result in improved efficacy. The EPR2 guidelines had recommended doubling the dose of ICS; however, EPR3 discouraged the use of doubling ICS doses and instead mentioned that "preliminary evidence indicates that quadrupling the dose of an ICS for 7 days, starting at the first appearance of worsening symptoms, may prevent exacerbations requiring oral systemic corticosteroids." The key concept acknowledged in this practice parameter is that each yellow zone episode may require a different amount of supplemental ICS dose to prevent progression. For that reason, symptom-driven ICS use and dynamic dosing are attractive alternative options. In this model, patients receive a larger amount of ICS as they experience increasing loss of asthma control and a smaller amount of ICS as control is achieved. The evidence for dynamic dosing appears to be more consistent to that supporting the scheduled use of increased ICS dose in 24 hours.

Methods for administration of dynamic dosing include (1) separate use of reliever (ie, SABA) and controller inhalers in combination and (2) use of single inhalers that contain a reliever (SABA or quick-onset long-acting β agonists [LABA] such as formoterol) and a controller that is used for symptom relief (with accompanying escalation in controller therapy). Although the 2 approaches are effective, the use of a single inhaler with a reliever (ie, formoterol) and controller (ie, AMD) is more convenient and has been widely studied and used in other countries. A recent evidence-based review demonstrated that the AMD strategy can decrease exacerbations requiring oral corticosteroids (OCSs) compared with current best-practice strategies, although the authors do not recommend use of this approach in children and adolescents younger than 18 years because large-scale studies have not been conducted in this age group. Notably, although inhalers with the

Guide for Developing an Asthma Action Plan

Patient Identifiers:

Asthma Severity (Step): **Asthma Control:** **ACT /CACT Score:**

Quick Reliever Medicine ***Use As-Needed in all Zones***

Albuterol 90 mcg inhaler: inhale 2 puffs every 4 hours as needed (use with a spacer) or
Levalbuterol 45 mcg inhaler: inhale 2 puffs every 4 hours as needed (use with a spacer) or
Albuterol 0.083% Neb Solution: inhale 1 dose by nebulizer every 4 hours as needed or
Levalbuterol Neb Solution: inhale 1 dose by nebulizer every 4 hours as needed

Green Zone / Daily Treatment Plan.

This is the "feeling good" zone, where you should be every day.

- 2 or fewer days/week of cough, wheeze or use of a quick reliever
- Normal sleep and usual activities without cough or wheeze

Daily Treatment: (based on the patient's severity and / or control)

Recommended medication(s) Dose Frequency Instructions

What to do for an Asthma Episode?

Step-up therapy if any of the following occur:

- An increase in cough, wheeze, or other asthma symptoms
- An increase is the use of Quick Reliever
- Cough or wheeze during sleep or with usual activities
- A decline in Peak flow rate of 15% (number) or more
- If Peak flow <80% of personal best (number) after use of a Quick Reliever
- Exposure to a known trigger (respiratory tract infection) or allergen

Next, determine whether you are in the yellow zone or red zone:

1. Use 2-4 puffs of quick reliever inhaler (or 1 nebulized quick reliever treatment) NOW.
2. You may repeat the Quick Reliever every 20 minutes up to 3 times in one hour
3. If you get relief, go to **Yellow Zone** If you get little or no relief, go to **Red Zone** .

*Continue Quick Reliever Medicine as needed in all Zones
***If you have trouble speaking and/or your fingernails or lips are blue, call 911**

Yellow Zone / Acute Loss of Asthma Control.

Scheduled Dosing	Dynamic Dosing	Adjustable Maintenance Dosing
Increase total ICS dose / 24 hrs (4 times dose given BID or QID)	Use ICS along with reliever (concomitant dose of ICS with each reliever dose)	ICS-Formoterol- AMD Therapy (symptom driven delivery)
May try another option for next episode if inadequate success	May try another option for next episode if inadequate success	May try another option for next episode if inadequate success

Recommended medication(s) Dose Frequency Instructions

Use quick reliever at a dose of 2-4 puffs via metered dose inhaler or nebulizer treatment every 4-6 hours (as needed) in addition to the escalated yellow zone treatment. If use exceeds 12 puffs per day, please contact your provider for further guidance

Red Zone.

You are in the Red Zone if you have any of the following:

- Cough or wheeze throughout the day
- Short-of-breath at rest or with talking or walking
- Chest is sinking in around the ribs or at the neck
- Quick Reliever use several times/day without adequate response

Take this medicine and continue Yellow Zone treatment:

Oral steroids

***Call the provider** at (____) _____ or seek medical attention
***If you have trouble speaking and/or your fingernails or lips are blue, call 911**

Figure 2. Schematic guide for creating an asthma action plan. This schema is based on the options reviewed in this practice parameter. ACT, asthma control test; AMD, adjustable maintenance dosing; BID, twice daily; CACT, childhood asthma control test; ICS, inhaled corticosteroid; Nob, nebulized; QID, four times daily.

desired properties (ie, ICS with formoterol) are available in the United States, the FDA has not approved those inhalers for dynamic dosing or AMD therapy. In fact, the FDA specifically cautions against initiating use, or increasing the dose, of these inhalers during periods of acutely worsening asthma symptoms. As a result, these treatment options for yellow zone management of patients with asthma would be considered "off-label" in the United States, to be prescribed at the discretion and medical judgment of the individual provider, with additional extra caution to be exercised when using them in patients younger than 18 years.

The practice parameter concludes by briefly discussing additional approaches with limited or no evidence. Although these approaches may be beneficial for individual patients in special circumstances, they are not recommended for general use.

It is the hope of the Yellow Zone Workgroup that routine use of an effective yellow zone intervention for patients as part of an action plan will lead to decreased morbidity and improved quality of life for individuals with asthma. This document also highlights evidence gaps in yellow zone asthma management and strongly recommends conducting clinical trials to further validate the approaches explored in this document and to examine other effective options.

Introduction

Asthma guidelines recommend that patients with asthma be given an asthma action plan to provide direction in the event of loss of asthma control.[4] Asthma action plans typically follow a "traffic light" model, namely the green zone (asthma doing well), the yellow zone (asthma deterioration detected, intervention needed), and the red zone (asthma exacerbation requiring urgent treatment).

The EPR2 recommended doubling doses of ICS when patients entered the yellow zone.[5] However, in the 2007 update, the EPR3 did not include that recommendation because there was insufficient evidence to support this approach.[6] Instead, the intervention recommended in the EPR3 for home management of an asthma exacerbation was to step-up use of SABA and add a short course of OCSs if there was inadequate improvement or worsening of symptoms. The evidence to support that approach was not provided, with the document focusing instead on therapy designed to achieve long-term maintenance of control.

Although long-term control is a desirable outcome of asthma management, the reality is that asthma is a labile illness, associated with morbidity when control is lost acutely in a short timeframe, reinforcing the importance of dynamic treatment modifications driven by an asthma action plan. It provides patients with a framework for responding to changes in asthma control occurring over very short intervals.

So why is identification and management of acute loss of asthma control so important? If an impending exacerbation is not recognized and treated, it could progress to a severe exacerbation and include an ED visit, hospitalization, or even death. Conversely, instructions for patients to take OCSs and seek medical attention at the first sign of loss of control are likely to result in overtreatment. Although the latter might ensure that patients are always treated quickly, such treatment is potentially associated with unnecessary medical intervention and usage, resulting in increased costs and medication side effects with resultant short- and long-term morbidity. A targeted approach in which signs of impending exacerbations are recognized early and treated effectively with minimal side effects and disruption to a patient's quality of life would be ideal.[7]

This practice parameter presents a framework for the management of acute loss of asthma control, referred to in this document as *yellow zone treatment,* in the home setting. In many cases, data supporting a single effective approach are not available and therefore various options are reviewed. The acute loss of asthma control often signals the risk of an impending asthma exacerbation. The yellow zone signifies the transition zone signaling the onset of loss of asthma control, prompting the patient to escalate asthma therapy in an attempt to prevent further deterioration of control. This loss of control in the yellow zone may occur over hours to days. An example of this acute loss of control is the deterioration of asthma that can occur as a consequence of a viral illness.

The chief goal in the management of acute loss of asthma control (yellow zone intervention) is to prevent progression to a full asthma exacerbation (referred to as the *red zone*; Figure 1). A full asthma exacerbation or red zone episode represents severe loss of asthma control with symptoms and lung function deterioration that have progressed to the extent that systemic glucocorticoids or other acute asthma interventions such as ED visits are required to restore clinical stability and regain asthma control. The OCSs have been shown to be effective for treatment of most red zone asthma exacerbations if started early.[8,9] However, their palatability and side effects, especially if repeated courses are given, limit their use in the yellow zone. In addition, for those children who have several RTIs during a single respiratory viral season, parents are often reluctant to use OCSs for each of these episodes, because repeated courses of OCSs can be associated with significant side effects,[10–13] and recent studies have suggested that systemic corticosteroids may not provide clinical benefit in preschool children with acute wheezing episodes.[14,15]

The definition of acute loss of asthma control in the yellow zone should distinguish it from occasional asthma symptoms that do not indicate an impending exacerbation (eg, exercise-induced bronchospasm) and from severe asthma symptoms that require administration of OCSs and immediate medical attention. Because there is generally a narrow window of opportunity for a yellow zone intervention to work, early identification of symptoms and aggressive intervention may optimize the chances for a good outcome. Therefore, although a "false" start may lead to the initiation of yellow zone treatment when it may not be needed, the risk of a "late" start may result in episode progression and the need for treatment with systemic corticosteroids.

Strategies geared toward recognition of acute loss of asthma control in the yellow zone and therapeutic maneuvers to address them are reviewed in this practice parameter. The recommendations are based on a thorough and critical review of the medical literature, and in situations where data are lacking, options are presented. A schematic guide for developing an asthma action plan based on the options discussed in this practice parameter is illustrated in Figure 2.

Asthma action plans

Summary Statement 1: Asthma action plans typically follow a "traffic light" model with green, yellow, and red zones. Provide patients with an asthma action plan (written and/or electronic) that includes instructions for recognition of loss of control and activation of the yellow zone intervention plan. (Recommendation: B Evidence)

All iterations of the NHLBI guidelines for asthma have emphasized the zone concept of asthma care based on the traffic light model. The green zone signifies the zone in which asthma is well controlled, the yellow zone is when the asthma starts getting worse, and the red zone is the medical alert zone (http://www.nhlbi.nih.gov/health/public/lung/asthma/actionplan_text.htm). Because the yellow zone signals onset of acute loss of asthma control and the potential for an impending asthma exacerbation, instructions for prompt recognition of the yellow zone and intervention measures should be included in a written individualized asthma action plan.

Evidence-based reviews have shown that providing patients with individual written asthma action plans can decrease symptoms and unscheduled use of health care resources.[16,17] A subsequent review has found that providing instructions that indicate when to increase ICS and when to begin a course of OCSs are key features for inclusion in such asthma action plans.[18] Although there is controversy regarding whether the mere act of providing patients with a written action plan improves outcomes, such as asthma quality measurements and hospital admissions,[19–22] written interventions individualized to patients' needs and understanding have been shown to be helpful. Self-management action plans have been shown to improve asthma-specific quality of life, because patients feel less anxious about the influence of asthma on their daily activities. In a survey of caretakers of children with asthma attending a general pediatric clinic in an inner city hospital, 75% reported being given an asthma action plan.[23] Nine of every 10 caretakers with an action plan reported the asthma action plan to be of value in managing exacerbations. Therefore, clinicians can empower patients to manage their symptoms effectively by developing an asthma action plan.

It is not uncommon for patients to, on their own, adjust their medications (relievers and controllers) when faced with increasing symptoms. Partridge et al[24] relied on structured interviews of 3,415 physician-recruited adults at least 16 years old with asthma in 11 countries to assess medication use, asthma control, and patients' ability to recognize and self-manage worsening asthma. A large majority (88%) judged they were "very or quite" confident of their ability to self-manage worsening asthma without a physician visit. Most (84%) had worsening asthma sometime in the past year and more than two thirds (68%) reported being able to identify signs predicting worsening. The patients responded to signs of impending worsening by increasing their mediation. In general, they used a SABA at the onset of symptoms (>4-fold increase in SABA inhalations) when symptoms were at their peak compared with baseline, with the ICS being increased later and to a lesser extent when symptoms were at their worst. When symptoms began to weaken, patients decreased their intake of their SABA and ICS. Interestingly, although only 29% of patients stated that they had been given an acute care plan that included stepping up their maintenance therapy with worsening asthma, 52% acknowledged that they had done so anyway. This study clearly demonstrates that patients implicitly are dynamic in their dosing of asthma medications and adjust their medications to match their symptom severity. They do so even without direction and inappropriately in some cases, reinforcing the importance of a physician-developed asthma action plan.

There is substantial variability in the literature concerning the period of increased symptoms that precedes an asthma exacerbation. In that same retrospective analysis,[24] the investigators found that patients reported a mean time from the first appearance to peak of symptoms of 5.1 days (range <30 minutes to >2 weeks) and a mean interval from the peak of symptoms to recovery of 6.2 days. In the Pediatric Asthma Controller Trial (PACT) in children 6 to 14 years of age, examination of the response to OCS therapy (a predefined protocol of a 4-day course of OCS) showed rapid improvement over the first 2 days followed by a more gradual improvement, with mean PEF back to pre-exacerbation PEF by day 14 and later. Although the study was designed to examine the predictors, rather than the natural history, of exacerbations, it did demonstrate that symptoms begin to increase 2 days before initiation of OCS (based on symptoms, albuterol use, and PEF decrease). These and other studies show that there is often a lead time (measured in days) to the peak of an exacerbation, reinforcing the premise that there is a potential window of opportunity to intervene with a yellow zone plan that is prescribed by a provider and initiated by a patient. It is important to remember that symptoms generally return to baseline sooner than objective measurements of lung function, and for this reason it may be prudent to continue yellow zone therapy for a period of 2 weeks. Further research is needed to determine optimal length of therapy; however, the available data would indicate that the yellow zone intervention should be introduced at the onset of symptoms or exposure to known triggers and continued until full recovery. The literature would indicate that full recovery of symptoms may take up to 2 weeks after their onset.

Summary Statement 2: Instruct patients to activate the yellow zone intervention plan when there is acute loss of asthma control in a setting outside a medical care facility such as at home. The yellow zone (or zone of acute loss of control) is defined as:

- An increase in asthma symptoms
- An increase in use of reliever medications
- A PEFR decrease of at least 15% or a PEFR lower than 80% of personal best
- The presence or increase in nocturnal asthma symptoms. (Strong Recommendation: B Evidence)

Different criteria have been proposed to identify the yellow zone that has not yet progressed to the red zone. These include at least 1 of the following: an increase in asthma symptoms (≥2 times per day) greater than baseline, asthma symptoms do not improve or recur (≤4 hours) after treatment with an inhaled SABA, in the presence of increase in nocturnal symptoms, and PEF decrease of at least 15% or lower than 80% of personal best.

The frequency of asthma symptoms that suggest loss of control depends in part on the frequency of symptoms at baseline. Although the NHLBI guidelines emphasize that physicians should strive to enable patients to achieve "complete" asthma control (ie, the patient has no symptoms) and that asthma in most patients does become well controlled with adoption of management strategies outlined in the NHLBI guidelines, the reality is that many still have troublesome symptoms or exacerbations periodically.[25] Hence, frequency and severity of baseline symptoms need to be considered when identifying acute loss of control.

The frequency and severity of asthma symptoms that predict an impending asthma exacerbation have not been clearly determined because each patient is different. The Baylor Rule of 2s has been used as an indicator of inadequate asthma control: "asthma symptoms or use of quick-relief inhaler more than Two times a week, wake up at night with asthma symptoms more than Two times a month, refill quick-relief inhaler more than Two times a year, peak flow drop more than 20% with asthma symptom."[26]

However, except for the PEF measurement, this approach focuses on chronic lack of control, is heuristic, and thus is not applicable as a criterion for identifying acute loss of control for initiating yellow zone treatment. For example, a patient who has daily symptoms may exceed the twice-a-day rate without experiencing an increased risk of an impending exacerbation. Other studies have included other measurements of decay as indicators of asthma exacerbation, such as symptom scores and inability to attend school or go to work for 2 consecutive days.[27]

An increase in use of reliever medications

Mild asthma symptoms that completely resolve after a single SABA treatment do not necessarily indicate loss of control or entrance into the yellow zone. Conversely, symptoms that respond incompletely to repetitive or frequent SABA treatments or require more intensive treatment (eg, OCSs) should be treated as a red zone episode. That leaves symptoms that respond to at least 1 SABA treatment but recur after some time (≤4 hours) as a marker of the yellow zone.[6]

In a study that relied on frequency of bronchodilator use as a criterion for an asthma exacerbation, the mean number of inhalations was smaller than 0.5 per day at baseline and increased to 4 inhalations per day 2 days later in patients experiencing an exacerbation.[27] Clearly, the magnitude of increase in the frequency of reliever β-agonist use that indicates a yellow zone entry needs to be individualized.

An increase in nocturnal symptoms

Asthma tends to be associated with symptomatic and physiologic worsening that often occurs at nighttime. This means that if a patient has an increase in symptoms, then that increase can occur at nighttime. The frequency of nocturnal symptoms that reliably predicts imminent loss of control has not been defined. Although the NHLBI guidelines suggest that symptoms that occur 2 nights per month should be used as a guide for long-term loss of control, this is not relevant to the shorter timeframe being discussed in this practice parameter. In a study by FitzGerald et al,[27] nocturnal awakenings, β-agonist use, and PEF decrease were the criteria used to predict an asthma exacerbation. Nocturnal awakenings increased from 10% to 40% in patients during the exacerbation and then immediately decreased to baseline by day 4 in the placebo group. However, nocturnal awakenings were not predictive of an exacerbation.

Two studies in children have suggested that nocturnal awakenings are often followed by several markers of asthma morbidity but do not reliably precede severe exacerbations. In a study of children 5 to 12 years of age with mild to moderate asthma treated with as-needed SABA alone, the occurrence of nocturnal awakening was noted in 1 of 3 children and was followed by a temporal increase in symptom scores and albuterol use and a decrease in PEFs.[28] However, because the study design excluded children who experienced an exacerbation requiring OCSs, it was not possible to determine the ability of nocturnal awakenings to predict a red zone exacerbation. Horner et al[29] noted that more than 70% of children with mild to moderate asthma experienced at least 1 nocturnal awakening requiring SABA over a 48-week period. These awakenings were most likely to occur outside exacerbation periods and served as poor predictors of exacerbations despite their clear association with subsequent increased albuterol use, school absences, and doctor visits. In contrast, in adults participating in the Formoterol and Corticosteroids Establishing Therapy (FACET), Tattersfield et al[30] showed an increase in nocturnal symptoms and a decrease in nocturnal PEFs over the 3 days preceding exacerbations requiring OSCs. Thus, the role of nocturnal awakenings as a predictor of an imminent severe asthma exacerbation appears to be of limited utility in children but may be a more reliable predictor in adults.

PEFR decrease of at least 15% or lower than 80% of personal best

The use of daily PEF measurements was extremely popular for many years but has fallen into disfavor recently because of evidence that their measurement in most patients is not necessarily a better predictor of exacerbations than simply observing the frequency and severity of symptoms.[31] Even so, PEF measurements have been used in some studies, are objective, and can work well for adults. Unfortunately, there are inconsistencies in the extent of decrease in PEF criteria among studies. PEF measurements that decreased by 15% were used in a study by Harrison et al[32] and a decrease to below 80% predicted on 2 consecutive days was used in the study by FitzGerald et al.[27] In the study by Harrison et al, a PEF decrease of 15% and a symptom score increase of 1 point from baseline were predictive of an impending exacerbation. The sensitivity and specificity of a 15% decrease in PEF as a predictor for the need for OCSs were 43% and 66%, respectively, in the study.[32]

The PEF measurements may be particularly helpful in patients who are poor perceivers of their symptoms.[33] In 1 study, 26% of patients with asthma had lower-than-normal perception of dyspnea. These patients with blunted perception of dyspnea had statistically significantly more ED visits, hospitalizations, near-fatal asthma attacks, and deaths over a 24-month follow-up period compared with patients with normal perception of dyspnea and those with high perception of dyspnea.

When examining the exacerbations that occurred during the FACET trial, the investigators found that the mean maximal decrease in the morning PEF was 16% to 20%.[30] This decrease was gradual, from day −10 to −3, followed by a more rapid decrease. The pattern of increase in symptoms scores and SABA use was similar, and inverse, to the decrease in PEF. The PEF variability was a more specific indicator of a severe exacerbation in their study, with each 1% increase in variability associated with an increase odds ratio of 1.023. Nevertheless, symptoms appeared to be a more sensitive indicator of a red zone exacerbation compared with the defined decrease in PEF of 30%. This finding corroborates the results of other studies that have found the use of symptoms to be as useful as changes in PEF in identifying impending exacerbations.[34]

In a post hoc analysis of the PACT study, which examined a group of 285 children (6–14 years old) with mild to moderate persistent asthma randomized to receive 48 weeks of ICS (100 μg of fluticasone propionate twice daily), combination therapy (100 μg of fluticasone propionate daily and salmeterol twice daily), or a leukotriene modifier (5 mg of montelukast each night), it was found that children with previous exacerbations requiring systemic corticosteroids appeared to represent a distinct phenotype that was at higher risk for a future exacerbation, even with prolonged use of controller therapy.[35] Although the investigators found that seasons other than summer represented periods of increased risk of exacerbation, analysis of diary cards demonstrated that harbingers of exacerbation only manifest no more than a day before the exacerbation. They also found that PEF monitoring did not enhance the predictive value for an exacerbation compared with symptoms alone.[34] Therefore, in-depth analysis of studies of asthma exacerbations suggests that symptoms are a sensitive guide to impending exacerbation in most patients. Use of PEFs and other objective measurements may be a valuable addition and should be individualized and reinforced in certain subgroups, such as those who are poor perceivers of dyspnea. Better surrogates are needed as a reliable indicator of loss of control.

Summary Statement 3: Instruct patients to activate the yellow zone plan at the onset of an upper respiratory tract infection if this is a previously identified trigger. (Strong Recommendation: B Evidence)

Many patients experience loss of asthma control when they develop an RTI. This is particularly common in children who may have RTIs as their only asthma trigger. Studies have used the strategy of starting intervention at the earliest signs of onset of an RTI[36] or waiting until asthma symptoms increase before instituting yellow zone treatment. Intermittent montelukast given at the first sign of an RTI has not been effective in preventing the progression to severe exacerbation requiring OCS[36] but has been associated with attenuation of clinical severity of the acute episodes measured by symptom severity and heath care usage[37] and is a recommended approach by the European Respiratory Society for episodic viral wheeze.[38] The beneficial effects of intermittent montelukast in this wheezing phenotype were detected only in children with a positive modified asthma predictive index,[36] further emphasizing the need to tailor the treatment according to disease phenotype. Given the episodic nature of this condition, the role of intermittent high-dose ICS therapy in children with recurrent, but not persistent, wheezing has been a topic of recent research. Intermittent high-dose fluticasone propionate (750 μg twice daily) beginning at the onset of an

upper RTI in preschool children with a history of recurrent wheezing triggered by viral infections was associated with a 50% decrease in the rate of exacerbations requiring OCS[39] but was accompanied by decreases in growth in height and weight gains. Although intermittent high-dose budesonide (1 mg twice daily for 7 days) was not found to be superior to placebo when given at the early signs of an RTI,[36] this regimen was comparable to daily low-dose budesonide (0.5 mg once daily) in rates of severe exacerbations.[40]

Loss of asthma control can occur without identifiable exposure to obvious triggers. Conversely, many patients can recognize situations that are known to trigger loss of asthma control such as allergen exposure to a furred pet[41] in a pet-allergic person. For patients with a history of asthma exacerbations after exposure to a specific trigger, early implementation of a yellow zone plan may decrease the likelihood of progression to red zone.

Summary Statement 4: Instruct patients to escalate asthma therapy when they experience a loss of asthma control that puts them in the "yellow zone." (Recommendation: B Evidence)

Once a patient experiences the onset of yellow zone symptoms, implementation of a yellow zone management strategy should commence without delay to prevent further deterioration of asthma control. The ideal pharmacologic intervention for treatment in this situation would have the following characteristics:

- Quick onset of action with relief of symptoms; ideally this should be rapid enough to prevent progression into the red zone, thereby avoiding the need for OCSs, ED visits, or hospitalization
- Reliable prevention of progression to the red zone
- Safe enough to initiate at home by the patient, with acceptable and minimal side effects with repeated use over time
- Convenient dosing schedule, with frequency and route of administration that are practical for patients to self-administer
- Easy-to-use portable device if a device is needed
- Cost effective, with cost of treatment justified by its potential benefit

The ideal treatment strategy has not been identified, and thus no single recommendation of a yellow zone intervention can be made. However, several approaches have been examined. Treatment strategies will be reviewed and stratified by the age of the patient (0–4, 5–12, and >12 years) because the pathophysiologic mechanisms, triggers, and responsiveness vary based on factors, such as age, asthma predictive index status, severity, impairment, risk, and delivery device. These strategies are described below.

Intervention strategies in the yellow zone

Acute loss of asthma control or yellow zone episodes can occur in 2 ways. It can occur over days after exposure to a known trigger, such as at the onset of a viral respiratory tract illness, or an acute short-term allergen (furry animals) or irritant (fireworks) exposure.[42] Yellow zone interventions to treat these kinds of episodes include scheduled dosing step-up interventions such as quadrupling or higher doses of ICS and adding moderate- to high-dose ICS in those not receiving a daily controller. The yellow zone intervention in such instances is introduced at the onset of symptoms or triggers (yellow zone criteria described above) and continued until full recovery, ranging from approximately 1 week before peak symptoms to approximately 2 weeks.

In some situations, acute loss of control occurs over a shorter timeframe, over hours or days. This day-to-day variability also may be considered a yellow zone because ineffectual recognition and treatment can lead to decreased asthma control, escalating to a red zone exacerbation. Yellow zone interventions geared toward addressing these episodes include dynamic-dosing step-up strategies with ICS and SABA and with ICS and LABA. Terms used for dynamic-dosing step-up strategies using ICS-LABA in various studies are AMD, maintenance and reliever use, and single-inhaler maintenance and reliever therapy. AMD in this document refers to these dynamic-dosing strategies.

Based on the information above, several strategies have been proposed for treatment of patients who are in the yellow zone:

- Repetitive use of inhaled SABA (current EPR 3 recommendation)
- Scheduled-dosing step-up
  - Increasing total ICS dose per 24 hours (at least quadrupling doses of ICS) (Option: B Evidence)
- Dynamic-dosing step-up
  - ICS and reliever SABA use (Option: B Evidence)
  - ICS and LABA AMD use (Option: B Evidence)

Summary Statement 5: Advise patients to use inhaled SABA for reliever use in the yellow zone at a dose of 2 to 4 puffs through a metered dose inhaler or nebulizer treatment every 4 to 6 hours in addition to their escalated yellow zone treatment. If use exceeds 12 puffs per day, advise patients to contact their provider for further guidance. (Recommendation: C Evidence)

Repetitive or scheduled use of SABA (current EPR 3 recommendation)

The 2007 NHLBI guidelines recommend 2 to 6 puffs of SABA through a metered dose inhaler or nebulizer treatments be given every 3 to 4 hours for 24 to 48 hours for home exacerbations of asthma (Figure 5-4 of the guidelines).[6] However, no evidence or explanation for the evidence category A recommendation is provided in the document. Although the 2011 Global Strategy for Asthma Management and Prevention guidelines do not have a section on "home management" of asthma exacerbations, their recommendations regarding asthma exacerbations in the community setting are for patients to receive 2 to 4 puffs of SABA every 20 minutes for 1 hour, 2 to 4 puffs every 3 to 4 hours if there is a good response with no additional treatment, and 6 to 10 puffs for a moderate exacerbation.[9]

There are many factors that may affect the bronchodilator efficacy of SABA during an asthma exacerbation. These include the presence and severity of airway inflammation and edema, duration of symptoms, triggering mechanism, prior β-agonist use, airway caliber, airway elasticity, route of medication delivery, and the outcome measurement used to evaluate response. A study of bronchodilator response to inhaled albuterol in children and adults with asthma using a population pharmacodynamic model demonstrated that 2 to 4 inhalations of albuterol can increase the forced expiration volume in 1 second (FEV_1) by 15% in moderate to severe disease.[43] A yellow zone exacerbation of asthma typically can be considered a mild or moderate asthma exacerbation. In a randomized, double-blinded, controlled study in an ED setting, different doses and delivery devices were compared (2 puffs, 6–10 puffs, and 0.15 mg of nebulized albuterol) in children 5 to 17 years of age.[44] No significant differences were seen among the 3 groups in measured outcomes (clinical score, percentage of predicted FEV_1, oxygen saturation, and respiratory score). There was a slight increase in adverse events (heart rate) in the group receiving nebulized treatment. The study results suggested that 2 puffs of albuterol through a metered dose inhaler supervised by trained medical personnel provided similar benefit to 6 puffs through a metered dose inhaler or nebulizer.

It should be noted that the delineation of yellow and red zone exacerbations based on the number of puffs of SABA have been extrapolated from clinical studies that have used these criteria. In the Treating Children to Prevent Exacerbations of Asthma (TREXA) trial that evaluated strategies to treat intermittent acute loss of

control, criteria used to define an exacerbation (red zone) included increased albuterol use to 12 puffs per day, a decrease in PEF to lower than 70% predicted, inability to sleep or perform daily activities for at least 2 days, a decrease in PEF by 50% after albuterol, or a visit to the ED due to worsening asthma symptoms.[45] The cutoff limit of more than 12 puffs per day in older children and adults and more than 8 puffs per day in younger children has been used in other clinical trials to define a red zone exacerbation.[45]

Summary Statement 6: Advise patients currently treated with daily low-to-moderate dose ICS therapy to increase the total ICS dose per 24 hours (ie, quadrupling) for managing loss of asthma control in the yellow zone. (Option: B Evidence)

Increasing the dose of ICSs has been explored as an intervention for the treatment of exacerbation of asthma in the yellow zone. However, this literature has been hampered by lack of control data regarding the timing of initiation of the added therapy, the optimal amount of escalation, frequency, duration of increase in dose, and variability in response based on asthma phenotype. Although studies have not demonstrated efficacy with doubling the dose of ICS, some recent studies have shown that quadrupling the dose of ICS appears to be effective.

Doubling the dose of ICS

Several studies have examined the role of increasing the ICS dose when worsening asthma symptoms develop in an attempt to prevent progression of symptoms to a severe exacerbation. Because previous National Asthma Education and Prevention Program guidelines, published in 1997,[46] are still followed by many practitioners, it is common practice to double the dose of ICS at the onset of exacerbations. Previous studies have suggested support for the success of this intervention, with 2 pediatric studies observing an improvement in symptom scores and parental preference for increased ICS in controlled studies[47,48] and 1 showing a marked decrease in OCS use and hospitalization with increasing doses of ICS.[49] However, several recent randomized controlled studies have failed to demonstrate that doubling doses of ICS in those already receiving ICS therapy is effective.[27,32,50,51]

The challenge in interpreting the studies on doubling doses of ICS in the yellow zone is related to limitations in study design.[27,32,50,51] A major criticism relates to the timing of the increase in ICS dosing. These trials have used different criteria to identify when to augment ICS therapy. The onset of an exacerbation has been commonly defined by decreases in PEF from baseline with or without symptom increases for a predetermined period, such as 48 hours in the study by FitzGerald et al[27] or 3 days in the study by Garrett et al.[50] However, it needs to be recognized that by the time such prolonged symptom onset or decreases in airway function are detected, the exacerbation is probably established, and the studied intervention may have decreased efficacy. Hence, deployment of an effective yellow zone intervention should be chronologically targeted to the kinetics of symptom increase in relation to the exacerbation, and future studies should consider using dose escalation at the first sign of lost control or soon after exposure to a known trigger.

It is also possible that the intervention of doubling the dose was incrementally too small to make a difference in someone already taking an adequate controller dose of ICS. Nevertheless, some clinicians and patients have reported that doubling doses of ICS, if timed right, seems to be effective in combating less severe episodes of acute loss of control. It also could be speculated that there may be phenotypic differences and disparities in response based on the triggers that dictate variation in response to the doubling ICS dose intervention in the yellow zone. There have not been any yellow zone studies involving commencement of ICS at the typical "doubling or higher ICS doses" performed in steroid-naive patients with asthma or those with intermittent asthma, and thus the response in this group is not known. In a study of 238 preschool children 12 to 59 months of age receiving intermittent therapy with ICS or leukotriene receptor antagonist, 1 mg of budesonide twice daily, 4 mg of montelukast daily, or placebo for 7 days was instituted at the first sign of a respiratory tract illness or other trigger individualized to the child.[36] There was no significant difference among the groups in number of episode-free days (primary outcome). However, there was significant improvement in control of symptoms in the leukotriene receptor antagonist and ICS groups of children with a positive modified asthma predictive index (and future risk for asthma) score or prior OCS use (propensity for greater illness severity) compared with the placebo group. Therefore, it is promising that the institution of a moderate or higher dose of ICS during a yellow zone exacerbation in young patients not on a daily controller may provide relief; however, further research is needed.

Quadrupling the dose of ICS

Although there are some data demonstrating efficacy of quadrupling doses of ICS, not all studies have demonstrated efficacy. This may be due to issues related to study design, such as timing of initiation of therapy, and the patient population studied.

The EPR3 guidelines state that preliminary evidence suggests that quadrupling the dose of an ICS for 7 days, starting at the first appearance of worsening symptoms, can prevent exacerbations.[6] In the study referenced in this document, patients with asthma, stabilized on 800 μg of budesonide twice daily, were randomized to receive 100 or 400 μg of budesonide twice daily with additional treatment when symptoms increased. Group 1 received 400 μg twice daily plus placebo, group 2 received 100 μg twice daily plus 200 μg 4 times daily, and group 3 received 100 mg twice daily plus placebo. The primary outcome was an asthma exacerbation defined by a decrease in PEF less than 70% from the baseline value, calculated during the last 2-week pretreatment period, on at least 2 consecutive days. Patients stratified to group 2 (quadrupling of their ICS at the onset of an exacerbation) had significantly smaller numbers of exacerbations and fewer days with exacerbations compared with group 3 (per-protocol analysis). In patients treated with the standard budesonide dose (group 1), the number of exacerbations and days with exacerbations were significantly decreased than in group 3 (intention-to-treat analysis).

A more recent trial by Oborne et al[52] investigated whether quadrupling the dose of ICS was an effective option for attenuating impending exacerbations. In addition to their usual asthma treatment, 403 patients at least 16 years old with current asthma stabilized on an ICS (200–1,000 μg of beclomethasone) were randomized to placebo or a quadrupled ICS dose in an inhaler used when predefined criteria for exacerbation were met. The intervention criteria were deteriorating asthma control, onset of an upper RTI, PEF decrease by 15% on 2 consecutive days, or PEF decrease by 30% on 1 day from the mean run-in the morning PEF. The primary outcome, OCS-requiring exacerbation, was decreased in the active group, but this was not statistically significant. Eighteen of 197 (9%) in the active group and 29 of 203 (14%) in the placebo group had an exacerbation of asthma requiring treatment with an OCS, for a risk ratio of 0.64 (95% confidence interval 0.37–1.11, $P = .11$). In the per-protocol analysis, quadrupling of ICS dosing when the PEF decreased by 15% on 2 consecutive days or by 30% on 1 day was associated with a risk ratio of 0.43 for requiring an OCS. In other words, in patients who were adherent to the study protocol (ie, administered their study inhaler), exacerbations were significantly decreased by more than 50%. These 2 studies indicate that quadrupling or higher doses of ICS for the yellow zone may be effective if the medication is augmented in a timely manner.

Another recent study attempting to investigate the efficacy of escalating doses of ICS to prevent asthma exacerbations in children found no difference in the need to institute systemic steroids

(primary outcome). Children with asthma 2 to 17 years old maintained on ICSs were randomly assigned to a 12-day treatment protocol for acute asthma exacerbation at doses of ICS that were 2, 4, or 8 times their maintenance ICS dose.[53] Criteria for initiating the step-up therapy included decrease in PEF to 50% to 80% of personal best, increasing cough present for 24 to 72 hours, or wheezing present for 24 to 72 hours that was responsive to β-agonist therapy. The secondary outcome was difference in symptom scores among the 3 treatment groups to determine whether 1 dosing protocol was superior to another. The daily maintenance dose ranged from 88 μg of fluticasone propionate and 500 μg of budesonide to 880 μg of fluticasone propionate and 1000 μg of budesonide. Patients randomized to the doubling dose of ICS served as controls because that recommendation was consistent with the previous iterations of National Asthma Education and Prevention Program guidelines[4] as standard of care for mild exacerbations. Eighty-two of 197 enrolled patients experienced an acute asthma exacerbation and completed the escalated dosing protocol. Four patients required treatment with systemic steroids in the study, 2 each from the 2-fold (8.3%) and 4-fold (6.7%) groups and none from the 8-fold group. Although no significant difference in systemic corticosteroid use was detected among the groups, likely a reflection of inadequate statistical power for this outcome, a trend toward a larger decrease in mean total symptom score with increasing ICS dose was observed at the end of the study. The investigators postulated that timing of the intervention (institution of intervention within 72 hours of onset of symptoms), possible spontaneous recovery to baseline, and questionable overtreatment of previous exacerbations with systemic steroids could explain improvement regardless of the ICS dose increase.

The concept of escalation in the steroid dose also could be considered in terms of an increase in dosing frequency. In a study exploring the influence of various ICS dosing regimens on asthmatic response, 34 patients using different treatment regimens of budesonide were compared (budesonide given once or twice daily, in the morning or morning and evening at doses of 400, 800, or 1,600 μg/d).[54] All patients received each of the treatment combinations for 2 weeks. Changes in PEFR, blood eosinophils, and serum cortisol levels increased approximately linearly with the logarithmic dose of budesonide ($P < .0005$); however, systemic effects of the drug were nonsignificant at low dosage. Overall, the once-daily regimen showed the best risk-to-benefit relations. The data suggest that decreases in dose frequency made with the hope of improving patient adherence are likely to lead to decreased medication efficacy. Titrating dosage in puffs per dose rather than doses per day may enable attainment of a better risk-to-benefit balance, and an increase in dosing frequency may lead to increased efficacy. These therapeutic considerations probably apply to some or all the other topically active steroids currently used to treat asthma and are an important consideration for future dose escalation studies at the onset of yellow zone decay.[55–57]

Summary Statement 7: For children younger than 6 years with recurrent wheezing and risk factors for subsequent asthma (ie, positive modified asthma predictive index), consider initiating high-dose ICSs or oral montelukast at the early signs of wheezing illnesses to decrease intensity of symptoms. (Option: B Evidence)

In preschool-age children with intermittent wheezing (ie, episodic viral wheeze) who demonstrate minimal to no symptom burden outside periods of an RTI, several trials have examined the episodic use of asthma controller therapy on asthma-relevant outcomes. Three small studies in the 1990s found that intermittent use of ICS (moderate to high doses) at the onset of upper RTI symptoms did not decrease the need for OCS rescue.[47,48,58]

More recently, however, 4 larger trials have examined episodic ICS use at the early signs of illness in an effort to prevent symptom and episode progression. It should be noted that several of these studies did not require the presence of the classic "yellow zone" lower respiratory tract symptoms, but rather focused on symptoms that serve as typical antecedents of wheezing exacerbations in young children, with a focus on early symptoms indicative of an upper RTI. This population likely had heterogeneous etiologies for wheezing. Therefore, future studies should stratify the population based on modified asthma predictive index status. Bacharier et al[36] found that starting high-dose ICS (1 mg of budesonide twice daily for 1 week) and albuterol at the earliest recognition of patient-specific early signs of illness did not decrease OCS use but did lessen symptom severity during episodes compared with use of albuterol alone. Ducharme et al[39] found that the initiation of high-dose ICS (750 μg of fluticasone propionate twice daily until resolution of cough and wheeze for 48 hours) at the first sign of an upper RTI decreased the odds of OCS use by approximately 50% but was associated with statistically significant decreases in rate of linear and weight growth. Zeiger et al[40] demonstrated that children who received the episodic use of high-dose ICS (1 mg of budesonide twice daily for 1 week) and albuterol at the earliest recognition of patient-specific early signs of illness experienced comparable frequencies of exacerbations requiring OCSs as those children who received daily low-dose ICS (0.5 mg of budesonide once daily for 12 months).

A recent study including children 1 to 4 years of age with asthma symptoms on at least 7 of 14 days during a run-in period demonstrated that the "as-needed" use of ICS (800 μg of beclomethasone) given when albuterol rescue was needed did not differ from daily ICS (400 μg of beclomethasone twice daily) in the time to first exacerbation requiring an OCS.[59]

Overall, these data indicate that the early episodic use of high-dose ICS therapy, particularly in children at high risk for asthma (ie, positive modified asthma predictive index), may decrease the symptomatology during acute illnesses, and although the approach studied by Ducharme et al[39] was effective in decreasing exacerbations requiring an OCS, the occurrence of growth effects may lessen the clinical appeal of this strategy. The recent demonstration that episodic high-dose ICS was comparable to daily low-dose ICS in risk of exacerbation suggests that this approach may serve as an alternative strategy to daily therapy but remains associated with a lower, but not 0, risk of exacerbation.

Summary Statement 8: For patients with mild to moderate asthma, consider recommending symptom-driven use of ICSs with concomitant inhaled β agonist for control of a yellow zone asthma exacerbation. (Option: B Evidence)

Dynamic dosing

Most trials investigating yellow zone management have focused on a period of scheduled step-up of predefined medications as discussed earlier. However, if the yellow zone is reframed as a period of acute loss of asthma control, intermittent and sustained temporary loss of control would be considered the yellow zone. Therefore, research evaluating intervention during very early signs of asthma worsening, as in the "as-needed" use of step-up in controller medications and reliever bronchodilator use, could be accepted as an AMD yellow zone strategy. Recently, there have been results supporting this strategy.

Symptom-driven ICS step-up, with or without SABA

Boushey et al[60] used the approach of as-needed ICS administration in patients with mild asthma who were not receiving daily ICS in the Improving Asthma Control Trial (IMPACT). Adults (n = 225) with EPR guideline-defined mild persistent well-controlled asthma (low doses of ICS) were randomized to (1) low-dose ICS (200 mg twice daily), (2) leukotriene receptor antagonist (20 mg of zafirlukast), or (3) placebo. Participants in all 3 groups instituted a

symptom-based action plan when predetermined criteria suggesting lack of control were met. The interventions consisted of open-label budesonide (800 mg twice daily) for 10 days or prednisone (0.5 mg/kg of body weight per day) for 5 days if asthma symptoms worsened. The placebo group can be considered as having received intermittent therapy that can be considered a yellow zone strategy. The 3 treatments produced similar increases in morning PEF (primary outcome) and similar rates of asthma exacerbations (secondary outcome). Compared with intermittent therapy or daily zafirlukast therapy, daily budesonide therapy produced greater improvements in pre-bronchodilator FEV_1, 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 FEV_1 or quality of life. Based on these results, the authors suggest that it is possible to treat mild persistent asthma with short intermittent courses of ICSs or OCSs taken when symptoms worsen.

Three recent studies, 2 in adults and 1 in children, evaluated the novel approach of stepping down therapy in patients well controlled on low doses of ICS (EPR3 step 2 care) to the use of ICS each time the patient used rescue SABA. Thus, patients had the option of using intermittent step-up therapy when required for symptom control in 1 of the trial arms, enabling them to receive not only a bronchodilator but also an antiinflammatory medication. In the Beclomethasone plus Salbutamol Treatment (BEST) study, Papi et al[61] examined 455 adult patients (18–65 years of age) with mild well-controlled asthma on 250 mg of beclomethasone twice daily. The patients were randomized to 1 of 4 groups: placebo twice daily plus 250 μg of beclomethasone plus albuterol as needed (as-needed combination prescription), placebo twice daily plus albuterol as needed (as-needed albuterol prescription), 250 μg of beclomethasone twice daily plus albuterol as needed (regular beclomethasone prescription), and 250 μg of beclomethasone plus albuterol single inhaler twice daily plus albuterol as needed (regular combination prescription). They found that symptom-driven use of beclomethasone and albuterol in a single inhaler was as effective as regular use of beclomethasone twice daily for the primary outcome (morning PEF). Notably, the number of exacerbations during the 6-month treatment was significantly smaller in the as-needed combination therapy group (0.74) compared with the as-needed albuterol therapy group (1.63) but was not significantly different from those in the groups receiving regular beclomethasone therapy (0.71) or regular combination therapy (1.76). The 6-month cumulative dose of ICS was lower in the as-needed combination group (approximately one fourth the daily prescription). This suggests that symptom-based use of ICS plus SABA is efficacious in the yellow zone if started early and that *as-needed* albuterol alone is not effective in preventing progression to the red zone.

A similar approach, using increased doses of ICS at the earliest signs of asthma worsening, was examined in 843 children 5 to 18 years of age in the TREXA trial.[45] In this study, the ICS and albuterol were delivered in separate inhalers (as opposed to the adult study in which the ICS and albuterol were in a single inhaler). Participants who had well-controlled asthma while receiving low-dose beclomethasone were randomized to 1 of 4 treatment groups: twice-daily beclomethasone with beclomethasone plus albuterol as rescue (combined group), twice-daily beclomethasone with placebo plus albuterol as rescue (daily beclomethasone group), twice-daily placebo with beclomethasone plus albuterol as rescue (rescue beclomethasone group), and twice-daily placebo with placebo plus albuterol as rescue (placebo group). The study's primary outcome was time to first exacerbation. In this 44-week trial, the frequency of exacerbations and treatment failure was significantly higher in the placebo group (49%) compared with the other 3 groups in which ICS was used as reliever and/or maintenance (28–35%). Interestingly, the secondary outcome, linear growth, was significantly worse in the combined and daily ICS arms compared with the rescue ICS arm, with growth being 1.1 cm (SD 0.3 cm) less in the combined and daily arms ($P < .00010001$) but not in the rescue arm ($P = .26$). The rescue group also received 15% to 25% of the ICS dose that those in the combined and daily ICS groups received. The investigators concluded that ICS as rescue medication with albuterol might be an effective step-down strategy for children with mild asthma that is well controlled with low-dose ICS.

The Best Adjustment Strategy for Asthma in the Long Term (BASALT) study also demonstrated that symptom-based ICS use is comparable to daily ICS use in adults with asthma. The innovation of BASALT was to couple the use of FDA-approved reliever and controller treatments in a symptom-driven adjustment strategy. This was a parallel, 3-group, placebo-controlled, multicenter, randomized controlled trial of 342 adults with mild to moderate controlled asthma assigned to 1 of 3 approaches of adjusting ICS therapy in adults with asthma (physician assessment; biomarker- and symptom-based adjustment).[62] For symptom-based adjustment, an ICS was taken with each albuterol rescue use, and for the other 2 arms the dose of ICS was adjusted every 6 weeks based on measurements of control. Similar to the results of the IMPACT and BEST trials regarding rescue ICS use with symptoms compared with other interventions in patients with mild and mild to moderate persistent asthma, respectively, there were no significant differences in time to treatment failure.

Dynamic-dosing step-up with ICS plus albuterol may be considered an option for children (step 2) and adults whose asthma is mildly persistent (step 2 care per EPR3 guidelines).

Dynamic-dosing step-up: AMD

Dynamic-dosing step-up strategies using combination therapy with an ICS and a LABA have been studied by different research groups. Although the traditional fixed-dose strategy is designed to allow the patients to maintain complete control, the AMD strategy encourages the patient to escalate extra dosing based on symptoms. This may enable a decrease in cumulative controller dose and avoidance of OCSs. Other terms used for this dynamic-dosing step-up strategy using ICS and LABA in various studies reviewed below are maintenance and reliever use and single-inhaler maintenance and reliever therapy. As mentioned earlier in the document, AMD is used in this document to ensure consistency.

Multiple recent studies have consistently demonstrated efficacy of AMD in the treatment of the yellow zone. Hence, this AMD therapy has become standard of care in many countries in Europe and Canada. However, it is to be noted that these studies used doses that exceed the FDA approval (up to 3 times the recommended dose) and the Turbuhaler (AstraZeneca, London, United Kingdom) device is approved for use in these countries.[63] These medications are available for use in the United States in as metered dose inhalers and there is an FDA boxed warning regarding the use of the LABA component of this regimen. Evidence for use of this AMD strategy will be critically reviewed below.

Initial open-label studies suggested that patient-driven AMD with an ICS-LABA combination may provide better symptom control, fewer exacerbations, and better cost effectiveness.[64,65] However, the first controlled trial of fixed vs AMD doses in adults with persistent asthma came to a different conclusion. FitzGerald et al[66] compared fixed dosing with fluticasone and salmeterol (250 and 50 mg twice daily) vs AMD with budesonide and formoterol (400 and 12 mg twice daily). After a run-in period with each of these dosing strategies, patients in the budesonide-formoterol arm halved their dose. Then, they were instructed to increase or decrease the numbers of puffs per day based on the following measurements of control: nocturnal awakenings caused by asthma, frequency of rescue medication use, and changes in morning PEF. The study findings were that after 48 weeks of therapy, patients receiving

stable dosing of 250 and 50 mg of fluticasone and salmeterol twice daily had significantly greater increases in symptom-free days, days free of rescue medication, and morning PEF. Notably, they also experienced almost a halving of the exacerbation rate compared with AMD with formoterol and budesonide. The investigators interpreted the data as suggesting that a minimum daily amount of maintenance therapy seemed to be necessary to prevent exacerbations in adults with persistent asthma.

Conversely, several other research groups have demonstrated favorable data supporting AMD strategies. Aalbers et al[67] found that AMD with budesonide and formoterol decreased exacerbations and reliever medication use compared with fixed-dose fluticasone and salmeterol. Using a single combination product (formoterol and budesonide) with an AMD strategy vs a fixed-dose strategy, Ind et al[68] found that AMD with budesonide and formoterol in a single inhaler provided effective asthma control at lower medication doses. Symptom control was maintained or improved in 85% to 86% of patients in the 2 groups, and 94% experienced no treatment failures.

The LABA formoterol is similar to SABA reliever medication in rapidity of onset of bronchodilation. The possibility of using intermittent, symptom-based use of combination products with ICS and formoterol that can serve as controller and reliever has been studied by numerous groups. The rationale of the AMD concept is that patients would need to possess a single inhaler for maintenance and reliever therapy, thereby simplifying their regimen. Furthermore, the ICS obtained with the additional doses might further lower the risk of exacerbations. As seen in the study by Partridge et al,[24] when participants are faced with an exacerbation, most increase SABA immediately and delay their increase of ICS. Therefore, AMD therapy may ensure prompt institution of anti-inflammatory therapy in addition to providing symptom relief. In addition, a symptom-driven approach allows an acknowledgement of adherence problems and is a strategy that is consistent with "real-world" practice.

Nevertheless, a symptom-driven approach assumes that patients are cognizant of worsening asthma symptoms. This is not always true because it has been reported that many patients with asthma fail to perceive their level of disease control.[69] This lack of perception is not well correlated with their knowledge about asthma or any obvious personal characteristics[69] and may be more common in those with more severe disease,[70] increased hyperresponsiveness, and lower lung function.[71] Furthermore, because symptom perception varies among people, a pure symptom-driven approach may not be feasible in a select subgroup (ie, poor perceivers of dyspnea). Success of this strategy would depend on an effective provider-patient partnership and education, including a written asthma action plan with instructions to increase the patient's dose at early signs of acute loss of control.

The AMD strategy has been evaluated in multiple studies.[72–74] In the STEAM study, patients with mild to moderate asthma received AMD with budesonide plus formoterol or budesonide (double the maintenance dose used in the AMD arm) and as-needed SABA.[72] After 6 months of treatment, patients in the AMD arm had significantly greater improvements in PEF from baseline compared with patients receiving budesonide and as-needed SABA (34.5 vs 9.5 L/min, $P < .001$). There also was a significantly lower risk of severe exacerbations in the AMD arm (54%, $P = .0011$). The investigators opined that this demonstrated that the AMD approach was superior at producing symptom relief with a lower overall medication dose.

The 1-year STEP study evaluated these 2 regimens in patients with a greater severity of asthma (83% severe).[74] The time to first severe exacerbation (hospitalization or ED treatment or systemic steroids owing to asthma worsening or a decrease in morning PEF to $\leq$70% of baseline on 2 consecutive days) was prolonged in the AMD arm compared with the budesonide arm ($P < .001$) and the risk of having a severe exacerbation was 39% lower ($P < .001$). The AMD group had 45% fewer severe exacerbations requiring medical intervention per patient compared with the budesonide group ($P < .001$) and the mean daily ICS dose was lower in the AMD group than in the budesonide group (466 vs 640 μg/d).

The 1-year STAY study compared 3 different regimens in children and adults with moderate asthma: budesonide plus as-needed SABA (terbutaline); budesonide and formoterol plus as-needed SABA; and AMD with budesonide and formoterol.[73] This multicenter clinical trial involved 2,760 4- to 80-year-old patients with asthma (FEV_1 60% to 100% of predicted value). The results suggested that AMD (mean daily budesonide dose of 240 μg/d in adults and 126 μg/d in children) significantly prolonged the time to first severe exacerbation compared with the other 2 regimens ($P < .001$). All treatments improved asthma symptoms as measured by a decreased need for reliever medication and fewer nights with awakenings. The AMD using budesonide and formoterol prolonged the time to the first severe exacerbation, resulting in a 45% to 47% lower exacerbation risk compared with the other 2 treatment options. The AMD regimen also prolonged the time to the second and third exacerbations requiring medical intervention, decreased severe exacerbation rates, and improved symptoms, awakenings, and lung function compared with the 2 fixed-dosing regimens. The observation was made that the timing of the increased ICS dose (AMD) was likely the key factor that contributed to the improved outcomes compared with the magnitude of the increase in the budesonide dose (4-fold).

The SMILE trial attempted to characterize the contribution of budesonide and formoterol as reliever therapy.[75] All patients in this 1-year study received budesonide and formoterol (1 inhalation twice daily) as maintenance treatment but were randomized to receive 1 of 3 different as-needed reliever regimens: additional inhalations with budesonide and formoterol, formoterol alone, or terbutaline alone. As in previous studies, time to first severe exacerbation was significantly increased in the AMD arm compared with the other 2 strategies ($P = .0048$ vs formoterol relief, $P < .0001$ for terbutaline relief) and the yearly exacerbation rate was decreased by 33% and 48%, respectively. However, the AMD strategy failed to improve the percentage of asthma control days or patient-reported quality of life, suggesting as-needed budesonide plus formoterol may have a greater role in mitigating exacerbations than on every-day asthma control.

The COMPASS was a 6-month, double-blinded study that compared a budesonide plus formoterol AMD with fluticasone plus salmeterol or budesonide plus formoterol (with rescue terbutaline) at a higher maintenance dose than used in previous trials.[76] The higher dose was used to address the speculation that maintenance ICS dosing in comparison arms of previous trials may have been inadequate. Although the primary outcome of time to first severe exacerbation was significantly lengthened by the AMD regimen ($P = .0034$ vs fluticasone plus salmeterol, $P = .023$ compared with budesonide plus formoterol) and patients had 28% to 39% fewer exacerbations, all treatments used in the study produced similar improvements in lung function and asthma control days. There also was no difference among the 3 treatments in the rate of mild exacerbations or in patient-reported quality of life. Mean daily doses of ICS were lowest in the AMD arm (755 μg/d of BDP equivalent compared with 1,000 μg/d in the other 2 arms), highlighting the ability of the AMD regimen to achieve a lower effective dose of ICS.

The COSMOS was a 1-year, open-label comparison of AMD using fluticasone plus salmeterol plus salbutamol as needed with AMD using budesonide plus formoterol.[77] Of note, reversibility was not an inclusion criterion in this study, thereby addressing the possibility that there may be a differential response in LABA responders. Providers were permitted to titrate maintenance doses in

accordance with normal clinical practice. Compared with the AMD group, single-inhaler maintenance and reliever therapy with budesonide plus formoterol significantly lowered the risk and rate of exacerbations (instantaneous risk decreased by 25%, exacerbation rate decreased by 22%). The ICS dose was similar in the 2 arms of the study (1,420 μg/d of beclomethasome dipropionate equivalent for budesonide and 1,402 μg/d for fluticasone), but patients in the AMD arm had significantly decreased as-needed medication use and increased odds of having low weekly levels of reliever medication use. Interestingly, there was no difference in patient-reported quality of life between the 2 groups.

In a recent 24-week trial undertaken at 4 primary health care practices and 1 hospital in New Zealand, patients (16–65 years old) with a recent asthma exacerbation were randomly assigned to an AMD strategy (2 actuations of 200 μg of budesonide plus 6 μg of formoterol twice daily with 1 additional actuation as needed) or a standard fixed-dose regimen (1–2 actuations of salbutamol as needed in addition to maintenance budensonide-formaterol [bud-form] twice daily).[78] Metered dose inhalers were monitored electronically to measure actual use of medication. The primary outcome was the proportion of participants with at least 1 high-use episode of a β agonist (>8 actuations per day of bud-form in addition to the 4 maintenance doses in the AMD group or >16 actuations per day of salbutamol in the standard group). No significant difference was noted between the AMD (n = 151) and standard (n = 152) groups in the proportion of participants with at least 1 high-use episode of a β agonist; there were fewer days of high use in the AMD group (mean 5.1 days [SD 14.3] vs 8.9 days [SD 20.9], $P = .001$). Of the patients who had at least 1 high-use episode, those in the AMD group had fewer days of high use without medical review (8.5 days [SD 17.8] vs 18.3 days [SD 24.8], $P = .001$). Participants in the AMD group had fewer severe asthma exacerbations (35 vs 66, $P = .004$).

LABA concerns

Despite these efficacy data, concerns regarding potential safety issues expressed by the FDA for LABA use,[79] detailed below, have influenced the lack of federal regulatory approval of this strategy. These and similar protocols have become standard of care in Canada and some countries in Europe. Given the safety and efficacy of the AMD approach as reflected in the data in this document, this approach may be considered an option for use in the yellow zone.

Currently, there is an FDA boxed warning in the United States regarding the use of the LABA component of this regimen. Use of the single ICS-LABA inhaler as a maintenance and reliever is not approved by the FDA at this time. The FDA strongly cautions that this medication "should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma" and that it "is not indicated for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm." They recommend that an inhaled SABA also be provided to the patient for treatment of acute symptoms, despite regular twice-daily (morning and evening) use of ICS-LABA for maintenance of asthma control.

The concerns of the FDA stemmed from a review of 3 prospective, randomized, placebo-controlled, double-blinded clinical studies of formoterol at dosages of 12 and 24 μg twice daily for the treatment of patients with asthma.[80] In their review, the investigators found that a larger number of patients treated regularly with 24 μg of formoterol twice daily had a serious asthma exacerbation than those on placebo. In the studies, stable regimens of orally inhaled or intranasal corticosteroids, oral theophylline, short-acting antihistamines, or allergen immunotherapy were allowed as applicable. In the first study, 4 of 135 adult patients (3%) who had been treated with 24 μg of formoterol twice daily for 12 weeks had a serious asthma exacerbation compared with none of 136 placebo-treated patients. In the second study, 5 of 136 patients (3.7%) treated with 24 μg of formoterol twice daily for 12 weeks had a serious asthma exacerbation compared with 2 of 141 placebo-treated patients (1.4%). In the third study, 11 of 171 pediatric patients (6.4%) treated with 24 μg of formoterol twice daily for 12 months had a serious asthma exacerbation compared with none of 176 placebo-treated patients. In the 2 12-week studies in adults and adolescents, the serious asthma exacerbation events occurred 10 days to 2.5 months after the initiation of treatment. In the 1-year pediatric study, the serious but nonfatal asthma exacerbations occurred from day 50 to day 297 of treatment.

In the studies exploring the AMD using budesonide plus formoterol, the study protocols typically permitted a maximum of 10 as-needed inhalations in adults and 7 as-needed inhalations in children in a single day (in addition to their daily maintenance treatment) before contacting the investigator. In the pediatric study by Bisgaard et al[81] (n = 106), fewer than 5% of patients in the study took this maximum dose and there were no serious adverse events.

In a study by O'Byrne et al,[73] 2,760 4- to 80-year-old patients with asthma (FEV_1 60–100% predicted) received 0.4 mg of terbutaline as SABA with 80 μg of budesonide plus 4.5 μg of formoterol twice a day or 320 μg of budesonide twice a day or 80 μg of budesonide plus 4.5 μg of formoterol twice a day with 80 and 4.5 μg as needed (budesonide-formoterol AMD). Children used a once-nocturnal maintenance dose. There were 495 episodes with an increase in as-needed medication to more than 4 inhalations per day over the baseline value in the AMD group, of which 37 were associated with an exacerbation; 1,347 episodes in the budesonide-SABA (bud-SABA) group, with 120 associated with an exacerbation; and 1,196 episodes in the bud-SABA group, with 96 associated with an exacerbation. There were 26, 142, and 161 episodes of increased as-needed use of more than 8 inhalations per day above baseline in the AMD, bud-form-SABA, and bud-SABA groups, respectively; of these, only 2 preceded an exacerbation in the maintenance and reliever use group compared with 17 and 23 in the bud-form-SABA and bud-SABA groups, respectively. There was no evidence for overuse of reliever bud-form. On average, 55% of days were free of reliever use in the maintenance and reliever use group. The mean number of as-needed doses of bud-form was 1 additional dose per day, consistent with other studies (ie, 50% of days with use of an average extra 1 inhalation per day). In addition, there were notably fewer episodes of high as-needed medication use (≥8 inhalations above baseline) in the AMD group compared with the fixed dosing groups. Maintenance and reliever use also was associated with only 2 severe exacerbations in the high-user subgroup compared with 17 to 23 severe exacerbations in the as-needed SABA group. The average daily dose of budesonide resulting from AMD use was 80 μg higher than for patients who used the bud-form for fixed maintenance only (bud-form-SABA group). Importantly, no additional drug-related adverse events were identified with the use of extra bud-form for relief in addition to maintenance.

In a study from New Zealand by Patel et al,[78] the AMD regimen resulted in higher ICS exposure (943.5 μg/d [1,502.5] vs 684.3 μg/d [390.5] of budesonide, ratio of means 1.22 [1.06–1.41], $P = .006$) but decreased OCS exposure (77.5 mg [240.5] vs 126.6 mg [382.1] of prednisone, $P = .011$), with no significant difference in composite systemic corticosteroid exposure (793.7 mg [893.1] vs 772.1 mg [1,062.7] of prednisone equivalent per year, 1.03 [0.86–1.22], $P = .76$).

A systematic review from the Cochrane Airways group compared regular formoterol plus ICS with ICS only (at the same dose) for risk of death and of other "serious adverse events."[82] With the addition of 6 new randomized controlled trials in adults, there were 20 randomized controlled trials with more than 10,000 adults and 7 randomized controlled trials with 2,788 children. In adults,

they found significantly fewer asthma-related serious adverse events in those taking regular formoterol and ICS compared with ICS alone and no significant difference in all-cause serious adverse events. In children, there were too few data and too few events to allow any clear conclusions to be drawn. Seven deaths of adults were reported in more than 13,000 people, with 1 related to asthma. The investigators summarized that no conclusions could be drawn about possible differences in the risk of death relating to taking ICS alone or with formoterol. Another recent Cochrane review has demonstrated that AMD strategy can decrease exacerbations requiring OCSs against current best-practice strategies and against a fixed higher dose of ICSs.[83] They found more discontinuations owing to adverse events on an AMD strategy compared with current best practice but no significant differences in serious adverse events. Limitations of the studies reviewed included the open-label design of the trials and inadequate information regarding adherence to treatment in the current best-practice arms of the trials. The authors do not recommend use of this approach in children and adolescents younger than 18 years because there is limited research evidence in this age group. Currently, there are there are several large clinical trials (adults, adolescents, and children) in the United States examining the risks of the ICS-LABA combination compared with ICS alone (http://www.clinicaltrials.gov). These studies are expected to provide valuable information on the safety aspects of regular use of low-dose LABA in combination with ICS but may not accurately reflect the risk of acute high-dose LABA (with ICS) in the setting of deteriorating asthma control.

Other less well-studied strategies

It should be noted that there is scant literature available regarding the use of alternative yellow zone interventions such as use of single-dose ICS, combination of SABA plus anticholinergics, and leukotriene modifiers. However, these options may be considered in individual cases at the discretion of the provider.

Single high dose of ICS. Because one of the potential concerns is the systemic effects of high-dose OCSs, use of 1 large dose of ICS might help minimize some side effects. In a study of mild asthma exacerbations, 19 patients were randomized to doubling the dose of ICS or adding a single dose of 3,200 μg of budesonide.[84] Those receiving the single high-dose treatment initially showed a greater increase in PEF in the first week (87.4 L/min [4.7] vs 76.7 L/min [5.3], $P = .029$). However, at 3 weeks, there was no difference between the groups.

SABA plus anticholinergics. There is controversy over the use of anticholinergic agents, such as ipratropium, as a reliever bronchodilator in the care of patients with acute asthma. Although bronchodilation has been demonstrated by blockade of resting cholinergic bronchomotor tone and inhibition of cholinergic bronchoconstriction, data suggest these anticholinergic agents provide less bronchodilation and slower onset of action than SABA.[85,86]

Studies examining the combined use of β_2 agonists plus ipratropium have shown variable results. A randomized study by Rebuck et al[87] found that the greatest improvement in FEV_1 occurred at 45 and 90 minutes after therapy with the combined use of ipratropium and fenoterol compared with either alone in 148 patients with asthma with acute exacerbations. In contrast, Karpel et al[88] reported no long-term benefit with combination therapy in patients with acute asthma in the ED setting. Although patients receiving the combination of albuterol plus ipratropium showed greater improvement in FEV_1 at 45 minutes, no sustained benefit was seen at 90 minutes compared with either agent alone. It should be noted that in most of these studies, a low dose of ipratropium was used.

Rodrigo and Rodrigo[89] reported added efficacy with 4 puffs of high-dose ipratropium therapy (21 μg per puff) and albuterol (120 μg per puff) in 1 inhaler every 10 minutes for 3 hours. In this study of 180 patients with an acute asthma exacerbation (red zone exacerbation), those who received combination therapy had greater improvements in PEF (20.5%) and FEV_1 (48.1%) compared with patients who received albuterol alone. The hospitalization rate decreased significantly to 39% for patients given albuterol alone and to 20% for patients given the albuterol-ipratropium combination. The patients most likely to benefit from the addition of high doses of ipratropium were those who had an FEV_1 of 30% or less of predicted and symptoms for at least 24 hours before ED presentation.

Montelukast. Three studies have examined the potential role of intermittent montelukast therapy in young children, with modest overall results. Robertson et al[37] studied children 2 to 14 years of age with intermittent asthma and found that montelukast started at the onset of an upper RTI or asthma symptoms and continued for at least 7 days resulted in modest decreases in health care usage and symptom severity but no effect on OCS use, episode duration, or SABA use. Bacharier et al[36] found that starting montelukast with albuterol at the earliest recognition of patient-specific early signs of illness in children 1 to 5 years of age with severe intermittent wheezing also did not decrease OCS use but did lessen symptom severity during episodes compared with use of albuterol alone. Valovirta et al[90] compared daily and episodic montelukast (treatment started with signs or symptoms consistent with an imminent cold or breathing problem) with placebo in children 6 months to 5 years of age with episodic wheezing and found no difference between the montelukast arm and placebo in the number of episodes culminating in an asthma attack over the 1-year study.

Future research

Although exacerbations of asthma are a very common problem, there is a surprising paucity of data regarding intervention in this situation. Further research is desperately needed in children and adults. When designing these studies, investigators should consider the potential impact of the dose, timing and frequency of escalation of the intervention, and the population being studied. Moreover, it is imperative that further research be undertaken to better define early predictors of asthma exacerbations (including markers of inflammation) and strategies to prevent airway remodeling.[91]

References

[1] Joint Task Force on Practice Parameters. Practice parameters for the diagnosis and treatment of asthma. *J Allergy Clin Immunol*. 1995;96:707–870 (Ia).

[2] Li JT, Pearlman DS, Nicklas RA, et al. Algorithm for the diagnosis and management of asthma: a practice parameter update: Joint Task Force on Practice Parameters. *Ann Allergy Asthma Immunol*. 1998;81:415–420 (IIa).

[3] Attaining optimal asthma control: a practice parameter. *J Allergy Clin Immunol*. 2005;116:S3–S11 (Ia).

[4] National Heart, Lung, and Blood Institute. Guidelines for the diagnosis and management of asthma. National Asthma Education Program. Expert Panel Report. *J Allergy Clin Immunol*. 1991;88:425–534 (Ia).

[5] EPR-2. *Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma (EPR-2 1997)*. NIH Publication No 97-4051. Bethesda, MD: US Department of Health and Human Services; National Institutes of Health; National Heart, Lung, and Blood Institute; National Asthma Education and Prevention Program; 1997.

[6] Expert Panel Report 3 (EPR-3): guidelines for the diagnosis and management of asthma—summary report 2007. *J Allergy Clin Immunol*. 2007;120(suppl): S94–S138 (Ia).

[7] Dinakar C, Reddy M. The yellow zone in asthma treatment: is it a gray zone? *Ann Allergy Asthma Immunol*. 2004;92:7–16. quiz 7, 79. (IV).

[8] Rowe BH, Spooner CH, Ducharme FM, Bretzlaff JA, Bota GW. Corticosteroids for preventing relapse following acute exacerbations of asthma. *Cochrane Database Syst Rev*. 2007;3:CD000195 (Ia).

[9] GINA—Global Strategy for Asthma Management and Prevention. http://wwwginasthmacom/GuidelinesResourcesasp. Published 2006. (Ia).

[10] Dolan LM, Kesarwala HH, Holroyde JC, Fischer TJ. Short-term, high-dose, systemic steroids in children with asthma: the effect on the hypothalamic-pituitary-adrenal axis. *J Allergy Clin Immunol*. 1987;80:81–87 (IIb).
[11] Dawson KL, Carter ER. A steroid-induced acute psychosis in a child with asthma. *Pediatr Pulmonol*. 1998;26:362–364 (IIIa).
[12] Kayani S, Shannon DC. Adverse behavioral effects of treatment for acute exacerbation of asthma in children: a comparison of two doses of oral steroids. *Chest*. 2002;122:624–628 (Ib).
[13] van Staa TP, Cooper C, Leufkens HG, Bishop N. Children and the risk of fractures caused by oral corticosteroids. *J Bone Miner Res*. 2003;18:913–918 (IIb).
[14] Panickar J, Lakhanpaul M, Lambert PC, et al. Oral prednisolone for preschool children with acute virus-induced wheezing. *N Engl J Med*. 2009;360:329–338 (Ib).
[15] Beigelman A, King TS, Mauger D, et al. Do oral corticosteroids reduce the severity of acute lower respiratory tract illnesses in preschool children with recurrent wheezing? *J Allergy Clin Immunol*. 2013;131:1518–1525 (IIa).
[16] Gibson PG, Powell H, Coughlan J, et al. Self-management education and regular practitioner review for adults with asthma. *Cochrane Database Syst Rev*. 2003;1:CD001117 (Ia).
[17] Thoonen BP, Schermer TR, Van Den Boom G, et al. Self-management of asthma in general practice, asthma control and quality of life: a randomised controlled trial. *Thorax*. 2003;58:30–36 (IIa).
[18] Gibson PG, Powell H. Written action plans for asthma: an evidence-based review of the key components. *Thorax*. 2004;59:94–99 (Ia).
[19] Burrill R, Carroll W. Towards evidence based medicine for paediatricians. Do written asthma action plans reduce hospital admissions? *Arch Dis Child*. 2009;94:742–743 (IV).
[20] Espinoza-Palma T, Zamorano A, Arancibia F, et al. Effectiveness of asthma education with and without a self-management plan in hospitalized children. *J Asthma*. 2009;46:906–910 (Ib).
[21] Sunshine J, Song L, Krieger J. Written action plan use in inner-city children: is it independently associated with improved asthma outcomes? *Ann Allergy Asthma Immunol*. 2011;107:207–213 (IIb).
[22] Morse RB, Hall M, Fieldston ES, et al. Hospital-level compliance with asthma care quality measures at children's hospitals and subsequent asthma-related outcomes. *JAMA*. 2011;306:1454–1460 (IIIa).
[23] Dinakar C, Van Osdol TJ, Wible K. How frequent are asthma exacerbations in a pediatric primary care setting and do written asthma action plans help in their management? *J Asthma*. 2004;41:807–812 (IIIa).
[24] Partridge MR, van der Molen T, Myrseth SE, Busse WW. Attitudes and actions of asthma patients on regular maintenance therapy: the INSPIRE study. *BMC Pulm Med*. 2006;6:13 (IIb).
[25] Bateman ED, Boushey HA, Bousquet J, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. *Am J Respir Crit Care Med*. 2004;170:836–844 (Ib).
[26] Rules of two, ©2011. Baylor Health Care System. http://www.baylorhealth.com/SPECIALTIESSERVICES/ASTHMA/Pages/Education.aspx. Accessed November 18, 2013.
[27] FitzGerald JM, Becker A, Sears MR, Mink S, Chung K, Lee J. Doubling the dose of budesonide versus maintenance treatment in asthma exacerbations. *Thorax*. 2004;59:550–556 (Ib).
[28] Strunk RC, Sternberg AL, Bacharier LB, Szefler SJ. Nocturnal awakening caused by asthma in children with mild-to-moderate asthma in the childhood asthma management program. *J Allergy Clin Immunol*. 2002;110:395–403 (IIIa).
[29] Horner CC, Mauger D, Strunk RC, et al. Most nocturnal asthma symptoms occur outside of exacerbations and associate with morbidity. *J Allergy Clin Immunol*. 2011;128:977–982.e1–2 (Ib).
[30] Tattersfield AE, Postma DS, Barnes PJ, et al. Exacerbations of asthma: a descriptive study of 425 severe exacerbations. The FACET International Study Group. *Am J Respir Crit Care Med*. 1999;160:594–599 (Ib).
[31] Bhogal S, Zemek R, Ducharme FM. Written action plans for asthma in children. *Cochrane Database Syst Rev*. 2006;3:CD005306 (Ia).
[32] Harrison TW, Oborne J, Newton S, Tattersfield AE. Doubling the dose of inhaled corticosteroid to prevent asthma exacerbations: randomised controlled trial. *Lancet*. 2004;363:271–275 (Ib).
[33] Magadle R, Berar-Yanay N, Weiner P. The risk of hospitalization and near-fatal and fatal asthma in relation to the perception of dyspnea. *Chest*. 2002;121:329–333 (IIa).
[34] Buist AS, Vollmer WM, Wilson SR, Frazier EA, Hayward AD. A randomized clinical trial of peak flow versus symptom monitoring in older adults with asthma. *Am J Respir Crit Care Med*. 2006;174:1077–1087 (Ib).
[35] Covar RA, Szefler SJ, Zeiger RS, et al. Factors associated with asthma exacerbations during a long-term clinical trial of controller medications in children. *J Allergy Clin Immunol*. 2008;122:741–747.e4 (IIb).
[36] Bacharier LB, Phillips BR, Zeiger RS, et al. Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing. *J Allergy Clin Immunol*. 2008;122:1127–1135.e8 (Ib).
[37] Robertson CF, Price D, Henry R, et al. Short-course montelukast for intermittent asthma in children: a randomized controlled trial. *Am J Respir Crit Care Med*. 2007;175:323–329 (Ib).
[38] Brand PL, Baraldi E, Bisgaard H, et al. Definition, assessment and treatment of wheezing disorders in preschool children: an evidence-based approach. *Eur Respir J*. 2008;32:1096–1110 (IV).
[39] Ducharme FM, Lemire C, Noya FJ, et al. Preemptive use of high-dose fluticasone for virus-induced wheezing in young children. *N Engl J Med*. 2009;360:339–353 (Ib).
[40] Zeiger RS, Mauger D, Bacharier LB, et al. Daily or intermittent budesonide in preschool children with recurrent wheezing. *N Engl J Med*. 2011;365:1990–2001 (Ib).
[41] Van Metre TE Jr, Marsh DG, Adkinson NF Jr, et al. Dose of cat (Felis domesticus) allergen 1 (Fel d 1) that induces asthma. *J Allergy Clin Immunol*. 1986;78:62–75 (IIIa).
[42] Thomas A, Lemanske RF Jr, Jackson DJ. Approaches to stepping up and stepping down care in asthmatic patients. *J Allergy Clin Immunol*. 2011;128:915–924; quiz 25–26.
[43] Blake K, Madabushi R, Derendorf H, Lima J. Population pharmacodynamic model of bronchodilator response to inhaled albuterol in children and adults with asthma. *Chest*. 2008;134:981–989 (IIIa).
[44] Schuh S, Johnson DW, Stephens D, Callahan S, Winders P, Canny GJ. Comparison of albuterol delivered by a metered dose inhaler with spacer versus a nebulizer in children with mild acute asthma. *J Pediatr*. 1999;135:22–27 (Ib).
[45] Martinez FD, Chinchilli VM, Morgan WJ, et al. Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2011;377:650–657.
[46] National Heart, Lung, and Blood Institute. *Guidelines for the Diagnosis and Management of Asthma. Expert Panel Report 2*. Bethesda, MD: National Institutes of Health; 1997 (Ia).
[47] Wilson NM, Silverman M. Treatment of acute, episodic asthma in preschool children using intermittent high dose inhaled steroids at home. *Arch Dis Child*. 1990;65:407–410 (IIb).
[48] Connett G, Lenney W. Prevention of viral induced asthma attacks using inhaled budesonide. *Arch Dis Child*. 1993;68:85–87 (Ib).
[49] Volovitz B, Nussinovitch M, Finkelstein Y, Harel L, Varsano I. Effectiveness of inhaled corticosteroids in controlling acute asthma exacerbations in children at home. *Clin Pediatr (Phila)*. 2001;40:79–86 (IIa).
[50] Garrett J, Williams S, Wong C, Holdaway D. Treatment of acute asthmatic exacerbations with an increased dose of inhaled steroid. *Arch Dis Child*. 1998;79:12–17 (Ib).
[51] Rice-McDonald G, Bowler S, Staines G, Mitchell C. Doubling daily inhaled corticosteroid dose is ineffective in mild to moderately severe attacks of asthma in adults. *Intern Med J*. 2005;35:693–698 (Ib).
[52] Oborne J, Mortimer K, Hubbard RB, Tattersfield AE, Harrison TW. Quadrupling the dose of inhaled corticosteroid to prevent asthma exacerbations: a randomized, double-blind, placebo-controlled, parallel-group clinical trial. *Am J Respir Crit Care Med*. 2009;180:598–602 (Ib).
[53] Yousef E, Hossain J, Mannan S, Skorpinski E, McGeady S. Early intervention with high-dose inhaled corticosteroids for control of acute asthma exacerbations at home and improved outcomes: a randomized controlled trial. *Allergy Asthma Proc*. 2012;33:508–513 (Ib).
[54] Toogood JH, Baskerville JC, Jennings B, Lefcoe NM, Johansson SA. Influence of dosing frequency and schedule on the response of chronic asthmatics to the aerosol steroid, budesonide. *J Allergy Clin Immunol*. 1982;70:288–298 (Ib).
[55] Pincus DJ, Beam WR, Martin RJ. Chronobiology and chronotherapy of asthma. *Clin Chest Med*. 1995;16:699–713 (IV).
[56] Pincus DJ, Humeston TR, Martin RJ. Further studies on the chronotherapy of asthma with inhaled steroids: the effect of dosage timing on drug efficacy. *J Allergy Clin Immunol*. 1997;100:771–774 (IIa).
[57] Pincus DJ, Szefler SJ, Ackerson LM, Martin RJ. Chronotherapy of asthma with inhaled steroids: the effect of dosage timing on drug efficacy. *J Allergy Clin Immunol*. 1995;95:1172–1178 (IIIa).
[58] Svedmyr J, Nyberg E, Thunqvist P, Asbrink-Nilsson E, Hedlin G. Prophylactic intermittent treatment with inhaled corticosteroids of asthma exacerbations due to airway infections in toddlers. *Acta Paediatr*. 1999;88:42–47 (Ib).
[59] Papi A, Nicolini G, Baraldi E, et al. Regular vs prn nebulized treatment in wheeze preschool children. *Allergy*. 2009;64:1463–1471 (Ib).
[60] Boushey HA, Sorkness CA, King TS, et al. Daily versus as-needed corticosteroids for mild persistent asthma. *N Engl J Med*. 2005;352:1519–1528 (Ib).
[61] Papi A, Canonica GW, Maestrelli P, et al. Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. *N Engl J Med*. 2007;356:2040–2052 (Ib).
[62] Calhoun WJ, Ameredes BT, King TS, et al. Comparison of physician-, biomarker-, and symptom-based strategies for adjustment of inhaled corticosteroid therapy in adults with asthma: the BASALT randomized controlled trial. *JAMA*. 2012;308:987–997.
[63] Symbicort® prescribing information. Taking Symbicort SMART is simple. AstraZeneca; 2014. http://www.symbicort.com/asthma/prescribing-information.html http://www.symbicort.co.nz/smart/taking_smart.php. Accessed April 30, 2014.
[64] FitzGerald JM, Sears MR, Boulet LP, et al. Adjustable maintenance dosing with budesonide/formoterol reduces asthma exacerbations compared with traditional fixed dosing: a five-month multicentre Canadian study. *Can Respir J*. 2003;10:427–434 (IIa).
[65] Stallberg B, Olsson P, Jorgensen LA, Lindarck N, Ekstrom T. Budesonide/formoterol adjustable maintenance dosing reduces asthma exacerbations versus fixed dosing. *Int J Clin Pract*. 2003;57:656–661 (Ib).
[66] FitzGerald JM, Boulet LP, Follows RM. The CONCEPT trial: a 1-year, multicenter, randomized, double-blind, double-dummy comparison of a stable dosing regimen of salmeterol/fluticasone propionate with an adjustable maintenance dosing regimen of formoterol/budesonide in adults with persistent asthma. *Clin Ther*. 2005;27:393–406 (Ib).
[67] Aalbers R, Backer V, Kava TT, et al. Adjustable maintenance dosing with budesonide/formoterol compared with fixed-dose salmeterol/fluticasone in moderate to severe asthma. *Curr Med Res Opin*. 2004;20:225–240 (Ib).

[68] Ind PW, Haughney J, Price D, Rosen JP, Kennelly J. Adjustable and fixed dosing with budesonide/formoterol via a single inhaler in asthma patients: the ASSURE study. *Respir Med*. 2004;98:464–475 (Ib).
[69] Laforest L, Van Ganse E, Devouassoux G, et al. Asthmatic patients' poor awareness of inadequate disease control: a pharmacy-based survey. *Ann Allergy Asthma Immunol*. 2007;98:146–152 (IIIa).
[70] Chetta A, Gerra G, Foresi A, et al. Personality profiles and breathlessness perception in outpatients with different gradings of asthma. *Am J Respir Crit Care Med*. 1998;157:116–122 (IIIa).
[71] Bijl-Hofland ID, Cloosterman SG, Folgering HT, Akkermans RP, van Schayck CP. Relation of the perception of airway obstruction to the severity of asthma. *Thorax*. 1999;54:15–19 (IIIa).
[72] Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma exacerbations: a randomised controlled, double-blind study. *Lancet*. 2006;368:744–753 (Ib).
[73] O'Byrne PM, Bisgaard H, Godard PP, et al. Budesonide/formoterol combination therapy as both maintenance and reliever medication in asthma. *Am J Respir Crit Care Med*. 2005;171:129–136 (Ib).
[74] Scicchitano R, Aalbers R, Ukena D, et al. Efficacy and safety of budesonide/formoterol single inhaler therapy versus a higher dose of budesonide in moderate to severe asthma. *Curr Med Res Opin*. 2004;20:1403–1418 (Ib).
[75] Rabe KF, Pizzichini E, Stallberg B, et al. Budesonide/formoterol in a single inhaler for maintenance and relief in mild-to-moderate asthma: a randomized, double-blind trial. *Chest*. 2006;129:246–256 (Ib).
[76] Kuna P, Peters MJ, Manjra AI, et al. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. *Int J Clin Pract*. 2007;61:725–736 (Ib).
[77] Vogelmeier C, D'Urzo A, Pauwels R, et al. Budesonide/formoterol maintenance and reliever therapy: an effective asthma treatment option? *Eur Respir J*. 2005;26:819–828 (Ib).
[78] Patel M, Pilcher J, Travers J, et al. Use of metered-dose inhaler electronic monitoring in a real-world asthma randomized controlled trial. *J Allergy Clin Immunol Pract*. 2013;1:83–91 (IIa).
[79] Chowdhury BA, Seymour SM, Levenson MS. Assessing the safety of adding LABAs to inhaled corticosteroids for treating asthma. *N Engl J Med*. 2011;364:2473–2475 (IV).
[80] Mann M, Chowdhury B, Sullivan E, Nicklas R, Anthracite R, Meyer RJ. Serious asthma exacerbations in asthmatics treated with high-dose formoterol. *Chest*. 2003;124:70–74 (IIIa).
[81] Bisgaard H, Le Roux P, Bjamer D, Dymek A, Vermeulen JH, Hultquist C. Budesonide/formoterol maintenance plus reliever therapy: a new strategy in pediatric asthma. *Chest*. 2006;130:1733–1743 (Ib).
[82] Cates CJ, Lasserson TJ. Regular treatment with formoterol and an inhaled corticosteroid versus regular treatment with salmeterol and an inhaled corticosteroid for chronic asthma: serious adverse events. *Cochrane Database Syst Rev*. 2010;1:CD007694 (Ia).
[83] Cates CJ, Karner C. Combination formoterol and budesonide as maintenance and reliever therapy versus current best practice (including inhaled steroid maintenance), for chronic asthma in adults and children. *Cochrane Database Syst Rev*. 2013;4:CD007313 (Ia).
[84] Leuppi JD, Downie SR, Salome CM, Jenkins CR, Woolcock AJ. A single high dose of inhaled corticosteroids: a possible treatment of asthma exacerbations. *Swiss Med Wkly*. 2002;132:7–11 (Ib).
[85] Chapman KR. Anticholinergic bronchodilators for adult obstructive airways disease. *Am J Med*. 1991;91:13S–16S (Ib).
[86] Qureshi F, Pestian J, Davis P, Zaritsky A. Effect of nebulized ipratropium on the hospitalization rates of children with asthma. *N Engl J Med*. 1998;339:1030–1035 (IIa).
[87] Rebuck AS, Chapman KR, Abboud R, et al. Nebulized anticholinergic and sympathomimetic treatment of asthma and chronic obstructive airways disease in the emergency room. *Am J Med*. 1987;82:59–64 (IIIa).
[88] Karpel JP, Schacter EN, Fanta C, et al. A comparison of ipratropium and albuterol vs albuterol alone for the treatment of acute asthma. *Chest*. 1996;110:611–616 (Ib).
[89] Rodrigo GJ, Rodrigo C. First-line therapy for adult patients with acute asthma receiving a multiple-dose protocol of ipratropium bromide plus albuterol in the emergency department. *Am J Respir Crit Care Med*. 2000;161:1862–1868 (IIa).
[90] Valovirta E, Boza ML, Robertson CF, et al. Intermittent or daily montelukast versus placebo for episodic asthma in children. *Ann Allergy Asthma Immunol*. 2009;106:518–526.
[91] Grainge CL, Lau LC, Ward JA, et al. Effect of bronchoconstriction on airway remodeling in asthma. *N Engl J Med*. 2011;364:2006–2015 (Ib).