MANAGEMENT OF ACUTE LOSS OF ASTHMA
CONTROL IN THE YELLOW ZONE: A PRACTICE PARAMETER

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.

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There may frequently be a separation between the strength of recommendation and quality of evidence.
**Recommendation Rating Scale**

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<thead>
<tr>
<th>Statement</th>
<th>Definition</th>
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<tr>
<td>Strong recommendation</td>
<td>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.</td>
<td>Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present.</td>
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<tr>
<td>Recommendation</td>
<td>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.</td>
<td>Clinicians should also generally follow a recommendation but should remain alert to new information and sensitive to patient values and preferences.</td>
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<td>Weak Recommendation</td>
<td>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.</td>
<td>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.</td>
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<tr>
<td>No recommendation</td>
<td>No recommendation means there is both a lack of pertinent evidence (Grade D)* and an unclear balance between benefits and harms.</td>
<td>Clinicians should feel little constraint in their decision making and be alert to new published evidence that clarifies the balance of benefit versus harm; patient preferences and values should have a substantial influencing role.</td>
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<td>(NoRec)</td>
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Ia Evidence from meta-analysis of randomized controlled trials

Ib Evidence from at least one well-designed randomized controlled trial

Ic Evidence from at least one randomized controlled trial that was not very well designed

IIa Evidence from at least one controlled study without randomization

IIb Evidence from at least one other type of quasi-experimental study

IIc Evidence from one of the above that was not very well designed

IIIa Evidence from well-designed non-experimental descriptive studies, such as comparative studies

IIIb Evidence from non-experimental 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

Summary of Conflict of Interest 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.

<table>
<thead>
<tr>
<th>Work Group Member</th>
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Resolution of Potential Conflicts of Interest

The Joint Taskforce 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 Taskforce and any apparent bias is removed at that level.

Finally, the practice parameter is sent for review both 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.

How this practice parameter was developed

The Joint Taskforce on Practice Parameters (JTF)

The Joint Taskforce on Practice Parameters is a 13-member taskforce consisting of 6 representatives assigned by the American 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 taskforce oversees the development of practice parameters; selects the workgroup chair(s), 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 to be experts in the field of asthma management. Workgroup members have been vetted for financial conflicts of interest by the JTF and their COIs have been listed in this document and are posted on the JTF web site at http://www.allergyparameters.org. Where a potential COI is 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 Joint Task Force on Practice Parameters 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 we review the literature, relying upon medline and pubmed referenced publications, 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 or hospital settings.

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 escalate asthma therapy when there is loss of asthma control as defined by:

- An increase in asthma symptoms
- An increase in use of rescue medications
- A peak flow rate (PEFR) decline of 15% or more OR PEFR at <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 SABA for rescue use in the yellow zone at a dose of 2-4 puffs every 4-6 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 low-moderate dose daily inhaled corticosteroid therapy to consider increasing the total ICS dose per 24 hours (e.g. quadrupling) for managing loss of asthma control in the yellow zone. (Option, B Evidence)

Summary Statement 7

For children less than 6 years of age with recurrent wheezing and risk factors for subsequent asthma (i.e. positive modified asthma predictive index), consider initiating high dose inhaled corticosteroids or oral montelukast at the early signs of wheezing illnesses to reduce symptoms (Option, B Evidence)

Summary Statement 8
For patients with mild-moderate asthma, consider recommending symptom-driven use of inhaled corticosteroids with concomitant inhaled beta-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 Guidelines in 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 to take action when control deteriorated. The Guidelines emphasized long-term management of asthma with treatment strategies aimed at variations in symptoms that occur on a time frame of months. Most patients with asthma additionally experience loss of control that occurs over much shorter time frames such as hours to days in response to exposure to acute triggers. An asthma action plan is the logical tool to instruct patients on how to recognize and respond to such rapid changes in control with the goal of preventing deterioration of control to the red zone, often necessitating use of systemic corticosteroids and/or urgent medical care.

Since there are currently no guidelines providing clear evidence-based instructions on the management of patients who experience short-term loss of control, this practice parameter was written with the intent of addressing the gap.

The first recommendation in this practice parameter is for patients with asthma to be given a written and/or electronic asthma action plan. While 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 healthcare provider.

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 rescue medications, a decline in their peak flow (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 are advised to take action.

The specific action to take depends on the severity of the episode and 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, a number of potential interventions have been studied and are discussed below.

Potential interventions for yellow zone treatment include repetitive use of short-acting beta₂ agonists (SABA), scheduled step up of an inhaled corticosteroid (ICS), and symptom-driven use of controller with reliever therapy, otherwise known as dynamic dosing. The regular use of SABA on a scheduled basis as the sole treatment for 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 could be advised to increase their total 24 hour ICS dose, for example, by four-fold. Increase in the frequency of ICS administration over 24 hours may also result in improved efficacy. The EPR-2 guidelines recommended doubling the dose of ICS; however, EPR-3 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 the document 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 or dynamic dosing are alternate options. The underlying concept is that patients receive more ICS as they experience greater loss of asthma control, and they receive less 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 (regardless of whether it is doubled or quadrupled).

Methods for administration of dynamic dosing include separate use of reliever and controller inhalers in combination as well as use of single inhalers that contain both a reliever and controller that is used for symptom relief. While both approaches are effective, the use of a single inhaler with a reliever and controller is more convenient and has been widely studied and used in other countries. Notably, while inhalers with the desired properties are available in the United States, the FDA has not approved those inhalers for this purpose. As a result, these treatment options for yellow zone management of patients with asthma would be considered "off-label" in the United States.
The practice parameter concludes by briefly discussing additional approaches for which there is limited or no evidence. Such approaches may be beneficial for individual patients in special circumstances, but 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 reduced morbidity from asthma, and improved quality of life for individuals with asthma. This document also highlights evidence gaps in yellow zone asthma management and strongly recommends conduct of clinical trials validating approaches recommended in this document and further investigation regarding 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 Diagnosis and Management of Asthma Expert Panel Report 2* recommended doubling doses of ICS when patients entered the ‘yellow zone’ (5). However, the 2007 update did not include that recommendation because there was insufficient evidence to support this approach (6). Instead, the intervention recommended in the 2007 update for home management of an asthma exacerbation was to step up use of short acting beta agonists (SABA), and add a short course of oral steroids 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.

While 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 time frame, 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 time 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 ED visit, hospitalization or even death. On the other hand, instructions for patients to take oral...
steroids and seek medical attention at the first sign of loss of control are likely to result in over-
treatment. While the latter might ensure that patients are always treated quickly, such treatment is
potentially associated with unnecessary medical intervention and utilization resulting in increased costs,
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 (here referred to as ‘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 emergency department visits are required to restore clinical stability
and regain asthma control. Oral steroids 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 oral
corticosteroids for each of the episodes, as repeated courses of oral corticosteroids can be associated
with significant side effects (10-13) and recent studies suggest 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 (e.g. exercise induced
bronchospasm) and from severe asthma symptoms that require administration of oral steroids and
immediate medical attention. Since 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, while 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 towards 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.

**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 the 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 where the asthma is well controlled. ‘Yellow zone’ occurs when the asthma starts getting worse and ‘red zone’ is the medical alert zone (http://www.nhlbi.nih.gov/health/public/lung/asthma/actionplan_text.htm ). Since 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 reduce symptoms and unscheduled use of healthcare resources (16, 17). A subsequent review found that providing instructions that indicate when to increase ICS and when to begin a course of oral corticosteroids are key features for inclusion in such asthma action plans (18). While there is controversy regarding whether the mere act of providing patients with a written action plan improves outcomes such as asthma quality measures and hospital admissions (19) (20-22), 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, as patients feel less anxious about the influence of asthma on their daily activities. In a survey of caretakers of asthmatic children
attending a general pediatric clinic in an inner city hospital, 75% reported being given an asthma action plan (23). Nine out of every ten caretakers with an action plan reported the asthma action plan to be of value in managing exacerbations. Clinicians therefore 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 (both relievers and controllers), when faced with increasing symptoms. Partridge et al. relied upon structured interviews of 3415 physician-recruited adults aged >=16 years with asthma in 11 countries to assess medication use, asthma control and patients’ ability to recognize and self-manage worsening asthma (24). A large majority (88%) felt they were “very or quite” confident of their ability to self-manage worsening asthma, without a physician visit. The majority (84%) had worsening asthma sometime in the past year and over two thirds (68%) reported being able to identify signs predicting worsening. The patients responded to signs of impending worsening by increasing their medication. In general, they used a SABA at the onset of symptoms (>4-fold increase in SABA inhalations) when symptoms were at their peak compared to baseline, with the ICS being increased later and to a lesser extent when symptoms were at their worst. When symptoms began to decline, patients reduced intake of both their SABA as well as ICS. Interestingly, even though only 29% of patients stated that they had been given an acute care plan that including 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 in terms of the time period of increased symptoms that precedes an asthma exacerbation. In that same retrospective analysis (24), the investigators found that patients reported a mean length of 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 PACT trial among children 6-14 years of age, examination of the response to oral steroid (OCS) therapy (a pre-defined protocol of a 4 day course of OCS), showed rapid improvement over the first 2 days, followed by a more gradual improvement with mean peak flow back to pre-exacerbation peak flow by day +14. 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 oral corticosteroids (based upon symptoms, albuterol use, peak flow drop). These and other studies reveal 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 provider-prescribed and patient-initiated. It is important to remember that symptoms generally return to baseline sooner than objective measures 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 till 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 escalate asthma therapy when there is loss of asthma control as defined by:

- An increase in asthma symptoms
- An increase in use of rescue medications
- A peak flow rate decline of 15% or more OR PEFR at <80% of personal best
- The presence or increase in nocturnal asthma symptoms

(Strong Recommendation, B Evidence)

A number of criteria have been proposed to identify the yellow zone that has not yet progressed to the red zone. These include one or more of the following: an increase in asthma symptoms (two or more times per day) greater than baseline, asthma symptoms do not improve or recur (within 4 hours or less) after treatment with an inhaled SABA, in the presence of increase in nocturnal symptoms, and peak flow decline of 15% or more or at <80% of personal best.

The frequency of asthma symptoms that suggest loss of control depends in part on the frequency of symptoms at baseline. While the NHLBI Guidelines emphasize that we should strive to enable patients to achieve "complete" asthma control (i.e. the patient has no symptoms), and the majority of patients do become well-controlled with adoption of management strategies outlined in the 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 predicts an impending asthma exacerbation has 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 peak flow measurement, this approach focuses on chronic lack of control, is heuristic, and thus not applicable as a criterion for identifying acute loss of control for initiating yellow zone treatment. A patient who has daily symptoms, for example, may exceed the twice a day rate without experiencing an increased risk of an impending exacerbation. Other studies have included other measures 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 rescue 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. On the other hand, symptoms that respond incompletely to repetitive or frequent SABA treatments or require more intensive treatment (such as an oral corticosteroid) should be treated as a “red zone” episode. That leaves symptoms that respond to one or more SABA treatments but recur after a period of time (4 hours or less) as a marker of “yellow zone” (6).

In a study that relied upon frequency of bronchodilator use as a criterion for an asthma exacerbation, the mean number of inhalations was less than 0.5 per day at baseline, and increased to 4 inhalations per day two days later in patients experiencing an exacerbation (27). Clearly, the magnitude of increase in the frequency of rescue beta-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 physiological worsening that often occurs at nighttime. This means that if a patient has an increase in symptoms, that increase may occur at nighttime. The frequency of nocturnal symptoms that reliably predicts imminent loss of control has not
been defined. While 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 time frame being
discussed in this practice parameter. In a study by Fitzgerald et al, nocturnal awakenings, beta-agonist
use and peak flow decline were the criteria used to predict an asthma exacerbation. Nocturnal
awakenings increased from 10% to 40% of patients during the exacerbation and then immediately
decayed to baseline by day 4 in the placebo group. However, nocturnal awakenings were not predictive
of an exacerbation (27).

Two studies in children suggest that nocturnal awakenings are often followed by several markers of
asthma morbidity, but do not reliably precede severe exacerbations. In a study of children 5-12 years of
age with mild-moderate asthma treated with as needed SABA alone, the occurrence of nocturnal
awakening was noted in 1/3 of children and was followed by a temporal increase in symptoms scores
and albuterol use along with a decline in peak expiratory flows (28). However, since the study design
excluded children who experienced an exacerbation requiring oral corticosteroids, it was not possible to
determine the ability of nocturnal awakenings to predict a red zone exacerbation. Horner and colleagues
noted that >70% of children with mild to moderate asthma experienced at least one nocturnal awakening
requiring SABA over a 48-week period. These awakenings were most likely to occur outside of
exacerbation periods and served as poor predictors of exacerbations despite their clear association with
subsequent increased albuterol use, school absences, and doctor visits (29). In contrast, among adults
participating in the FACET trial, Tattersfield and colleagues demonstrated an increase in nocturnal
symptoms and a decline in nocturnal PEFs over the 3 days preceding exacerbations requiring oral
corticosteroids (30). 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 among
adults.

**A peak flow rate- decline of 15% or more or at <80% of personal best.**

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

Peak flow measurements may be particularly helpful in patients who are poor perceivers of their symptoms (33). In one study, 26% of patients with asthma had lower-than-normal perception of dyspnea. These patients with blunted perception of dyspnea had statistically significantly more emergency department (ED) visits, hospitalizations, near-fatal asthma attacks, and deaths over a 24-month follow-up period compared to the normal-POD and high-POD groups.

When examining the exacerbations that occurred during the FACET trial, the investigators found that the mean maximal fall in AM PEF was 16-20% (30). This fall was gradual, between day -10 to -3, followed by a more rapid decline. The pattern of increase in symptoms scores and SABA use was similar, and inverse, to the fall in peak flow. Peak flow 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. Despite this, symptoms appeared to be a more sensitive indicator of a red zone exacerbation compared to the defined fall in peak flow of 30%. This finding corroborates the results of other studies that have found the use of symptoms to be as useful as changes in peak flow in identifying impending exacerbations (34).

In a post-hoc analysis of the Pediatric Asthma Controller Trial (PACT) study, which examined a group of 285 children (6-14 yrs) with mild-to-moderate persistent asthma randomized to receive 48 weeks of ICS (FP 100ug BID), combination therapy (FP 100 ug QD and Salmeterol BID) or a leukotriene modifier (montelukast 5mg QHS), it was found that children with previous exacerbations requiring systemic corticosteroids appear to represent a distinct phenotype that were at higher risk for suffering a future exacerbation, even with prolonged use of controller therapy (35). Although the investigators found that seasons other than summer represented periods of increase risk of exacerbation, analysis of diary cards demonstrated that harbingers of exacerbation only manifest themselves a day or less prior to the exacerbation. They also found that peak flow monitoring did not enhance the predictive value for an exacerbation relative to symptoms alone(34). In-depth analysis of studies of asthma exacerbations therefore suggests that symptoms are a sensitive guide to impending exacerbation in most patients. Use of peak flows and other objective measures 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 a Respiratory Tract Infection (RTI). This is particularly common in children who may have RTIs as their only asthma trigger. Studies have either utilized the strategy of starting intervention at the earliest signs of onset of a RTI (36) or waiting until asthma symptoms increase before instituting yellow zone treatment. Intermittent montelukast given at the first sign of 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 healthcare utilization (37), and is a recommended approach by the ERS for episodic viral wheeze (38). The beneficial effects of intermittent montelukast in this wheezing phenotype were detected only among children with positive modified-API (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 among children with recurrent, but not persistent, wheezing has been a topic of recent research. Intermittent high dose fluticasone propionate (750 mcg of BID) beginning at the onset of an upper RTI among preschool children with history of recurrent wheezing triggered by viral infections was associated with a 50% reduction in the rate of exacerbations requiring OCS (39) but was accompanied by reductions in growth in terms of height and weight gains. While intermittent high dose budesonide (1 mg BID for 7 days) was not demonstrated to be superior to placebo when given at the early signs of an RTI (36), this regimen was comparable to daily low dose budesonide (0.5mg once daily) in terms of the rates of severe exacerbations (40).

Loss of asthma control can occur without identifiable exposure to obvious triggers. On the other hand, 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 individuals with a history of asthma exacerbations following exposure to a specific trigger, early implementation of a yellow zone plan may reduce 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 in an effort to prevent further deterioration of asthma control. The ideal pharmacological 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 red zone, thereby avoiding the need for oral steroids / ED visit/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 both frequency and route of administration that is 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 yellow zone intervention can be made. However, a number of approaches have been examined. Treatment strategies will be reviewed and stratified by the age of the patient (0-4 yrs, 5-12 years, > 12 years) since the pathophysiological mechanisms, triggers, and responsiveness vary based on factors such as age, asthma predictive index status, severity, impairment, risk, delivery device, among others. These strategies are described below.

**Intervention strategies in the Yellow Zone:**

Acute loss of asthma control or yellow zone episodes can occur in two 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-high dose ICS in those not receiving daily controller.
yellow zone intervention in such instances is introduced at onset of symptoms or triggers (Yellow Zone criteria described above) and continued until full recovery, ranging from about a week prior to peak symptoms to about 2 weeks.

In some situations, acute loss of control occurs over a shorter time frame, over hours or days. This day-day variability may also be considered as yellow zone since ineffectual recognition and treatment can lead to decay of asthma control triggering a red zone exacerbation. Yellow Zone interventions geared towards addressing these episodes include dynamic-dosing step-up strategies such as use of ICS along with rescue SABA and ICS-LABA Single-inhaler Maintenance and Reliever Therapy.

Based on the above, a number of strategies have been proposed for treatment of patients who are in the yellow zone. They include the following:

- Repetitive use of SABA (The Current EPR 3 recommendation)
- Scheduled-dosing Step-Up:
  - Increasing total ICS dose per 24 hours (e.g. Quadrupling or higher doses of ICS) (Option, B Evidence)
- Dynamic-dosing Step-Up:
  - ICS along with rescue SABA use (Option, B Evidence)
  - ICS-LABA- Single-inhaler Maintenance and Reliever Therapy use (Option, B Evidence)

Summary Statement 5. Advise patients to use SABA for rescue use in the yellow zone at a dose of 2-4 puffs every 4-6 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 (The Current EPR 3 recommendation)

The 2007 NHLBI guidelines recommend 2-6 puffs of albuterol be given every 3-4 hours for 24 to 48 hours for home exacerbations of asthma (Figure 5-4of the guidelines) (6). However, no evidence or explanation for the evidence Category A recommendation is provided in the document. Although the
2011 GINA 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 2-4 puffs of albuterol every 20 minutes for 1 hour, then 2-4 puffs every 3-4 hours if there is a good response with no additional treatment, and 6-10 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 beta-agonist use, airway caliber, airway elasticity, route of medication delivery, and the outcome measure 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 2-4 inhalations of albuterol can increase the FEV1 by 15% in moderate-severe disease (43). A yellow zone exacerbation of asthma typically can be considered a mild or moderate asthma exacerbation. In a randomized, double blind controlled study in an ED setting different doses and delivery devices were compared [2 puffs, 6-10 puffs, and nebulized albuterol (0.15 mg)] in children between 5-17 years of age (44). No significant differences were seen between the three groups in terms of the measured outcomes (clinical score, % predicted FEV1, O2 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 via MDI supervised by trained medical personnel provided similar benefit to 6 puffs via MDI or a nebulized treatment.

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 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 peak flow to less than 70% predicted, inability to sleep or do daily activities for 2 or more days, a decrease in peak flow by 50% after albuterol or a visit to the ED due to worsening asthma symptoms (45). The cut-off limit of >12 puffs per day in older children and adults and >8 puffs per day in younger children has been used in other clinical trials to define a red zone exacerbation (46).

**Summary Statement 6.** Advise patients currently treated with low-moderate dose daily inhaled corticosteroid therapy to increase the total ICS dose per 24 hours (e.g. quadrupling) for managing loss of asthma control in the yellow zone. (Option, B Evidence)
Increasing the dose of inhaled corticosteroids, has been explored as an intervention for the treatment of exacerbation of asthma in the yellow zone. This literature however, 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 upon the asthma phenotype. While studies have not demonstrated efficacy with doubling the dose of ICS, some recent studies show 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. Since previous NAEPP guidelines, published in 1997 (47), are still followed by many practitioners, it is common practice to double dose of ICS at the onset of exacerbations. Earlier, studies suggested support for the success of this intervention, with two pediatric studies observing an improvement in symptom scores and parental preference for increased ICS in controlled studies (48) (49), and one showing a marked decline in OCS use and hospitalization with increasing doses of ICS (50). However, several recent randomized controlled studies have failed to demonstrate that doubling doses of ICS in those already receiving ICS therapy to be effective (27) (51) (52).

The challenge in interpreting the studies on doubling doses of ICS in yellow zone is related to limitations in study design (27) (51) (52). 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 drop in PEFs from baseline with or without symptom increases for a pre-determined period of time, such as 48 hours in the Fitzgerald study, (27) and 3 days in the Garrett study (51). However, it needs to be recognized that by the time such prolonged symptom onset or declines in airway function are detected, the exacerbation is probably established, and the studied intervention may have reduced 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 employ dose escalation at first sign of decay 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 to someone already taking an adequate controller dose of ICS. Nevertheless, some clinicians
and patients report that doubling doses of ICS, if timed right, seems to be effective in combating less severe episodes of acute loss of control. It could also be speculated that there may be phenotypic differences and disparities of responses based on the triggers among patients that dictate their responses 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-naïve or intermittent asthmatics, and thus the response in this group is not known. In a study of 238 preschool children 12-59 months of age receiving intermittent therapy with ICS or LTRA, 1 mg budesonide bid, 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 between the groups in number of episode-free days (primary outcome). However, there were significant improvement in control of symptoms in both the LTRA and ICS groups in children with a positive modified asthma predictive index (and future risk for asthma) score or prior oral corticosteroid use (propensity for greater illness severity) compared to the placebo group. It is therefore promising that institution of moderate or higher dose ICS during a yellow zone exacerbation in young patients not on a daily controller may provide relief; however, research is needed.

**Quadrupling the dose of ICS**

Although there are some data demonstrating efficacy of quadrupling doses of ICS, not all studies demonstrated efficacy. This may be due to issues related to study design such as timing of initiation of therapy and 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 may prevent exacerbations (6). In the study referenced in this document, patients with asthma, stabilized on 800 ug budesonide bid, were randomized to receive 100 ug or 400 ug budesonide bid with additional treatment when symptoms increased. Group 1 received, 400 ug twice daily + placebo; group 2, 100 ug twice daily + 200 ug four times daily; group 3, 100 mg twice daily + placebo. The primary outcome was an asthma exacerbation defined by a fall in peak expiratory flow < 70% from 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 lower numbers of exacerbations as well as days with exacerbations, compared to 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 lower than in group 3 (intention-to-treat analysis).

A more recent trial by Oborne et al. investigated whether quadrupling the dose of ICS was an effective option for attenuating impending exacerbations (53). In addition to their usual asthma treatment, 403 subjects aged 16 years or older with current asthma stabilized on ICS (200-1000 mcg beclomethasone) were randomized to placebo or a quadrupled ICS dose in an inhaler used when predefined criteria for exacerbation was met. The intervention criteria were: if asthma control was deteriorating, onset of URTI, PEF decreased by 15% on 2 consecutive days, or PEF decrease by 30% on 1 day from mean run-in AM PEF. The primary outcome, oral corticosteroid-requiring exacerbation, was reduced in the active group, but this was not statistically significant. Eighteen of 197 (9%) in the active group, and 29 of 203 (14%) participants in the placebo group, had an exacerbation of asthma requiring treatment with oral corticosteroids giving a risk ratio of 0.64 (95% confidence interval, 0.37–1.11, \( P = 0.11 \)). In the per protocol analysis, quadrupling of ICS dosing when PEF fell by 15% on 2 consecutive days or 30% on 1 day was associated with a risk ratio of 0.43 for requiring oral corticosteroids. In other words, in patients who were adherent to the study protocol (ie, administered their study inhaler), exacerbations were significantly reduced by more than 50%. The above two 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 in attempt to prevent asthma exacerbations in children found no difference in the need to institute systemic steroids (primary outcome). Asthmatic children, aged 2-17 years, maintained on ICSs were randomly assigned to a 12-day treatment protocol for acute asthma exacerbation at doses of ICS that were two, four, or eight times their maintenance ICS dose (54). Criteria for initiating the step up therapy included: decrease in PEF to between 50-80% of personal best, increasing cough present for 24-72 hours, or wheezing present for 24-72 hours that was responsive to beta agonist therapy. The secondary outcome was difference in symptom scores among the three treatment groups to determine if one dosing protocol was superior to another. The daily maintenance dose ranged from 88 mcg of fluticasone propionate and 500 mcg of budesonide to 880 mcg of fluticasone propionate and 1000 mcg of budesonide. Patients randomized to the doubling dose of ICS served as controls since that recommendation was consistent with the earlier iterations NAEPP 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; two each from the twofold (8.3%) and fourfold (6.7%) groups, and none from the eightfold group. Though no significant difference in systemic corticosteroid use was detected between the groups, likely a reflection of inadequate statistical power for this outcome, a trend toward a larger reduction in mean total symptom score with increasing ICS dose was observed at the end of the study. The authors postulate 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 may explain improvement regardless of dose of ICS increase.

The concept of escalation in the steroid dose could also 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 utilizing different treatment regimens of budesonide were compared (Budesonide, given q.i.d. or b.i.d; in the morning or A.M./P.M; doses 400, 800, 1600/d) (55). All patients received each of the treatment combinations for 2 weeks. Changes in PEFR, blood eosinophils, and serum cortisol levels increased approximately linearly with log dose budesonide (p < 0.0005); however, systemic effects of the drug were non-significant at low dosage. Overall, the q.i.d. regimen showed the best risk-benefit relationships. The data suggest that reductions in dose frequency made with the hope of improving patient adherence are likely to lead to decreased medication efficacy. Titrating dosage in terms of puffs per dose rather than doses per day may enable attainment of a better risk/benefit balance, and increase in dosing frequency may lead to increased efficacy. These therapeutic considerations probably apply to some or all of 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 (56-58).

**Summary Statement 7:** For children less than 6 years of age with recurrent wheezing and risk factors for subsequent asthma (i.e. positive modified asthma predictive index), consider initiating high dose inhaled corticosteroids or oral montelukast at the early signs of wheezing illnesses to reduce symptoms (Option, B Evidence).

In preschool-aged children with intermittent wheezing (a.k.a. episodic viral wheeze), who demonstrate minimal to no symptom burden outside of periods of respiratory tract infection, 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-high dose) at the onset of URI symptoms did not reduce the need for OCS rescue (48) (49) (59).

More recently however, four 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 which serve as typical antecedents of wheezing exacerbations in young children, with a focus on early symptoms indicative of an upper respiratory tract infection. 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 found that starting high dose ICS (budesonide 1mg twice daily for 1 week) along with albuterol at the earliest recognition of patient-specific early signs of illness did not reduce OCS use but did lessen symptom severity during episodes relative to use of albuterol alone (36). Ducharme and colleagues found that the initiation of high dose ICS (fluticasone propionate 750mcg twice daily until resolution of cough and wheeze for 48 hours) at the first sign of a URI reduced the odds of OCS by approximately 50% but was associated with statistically significant reductions in rate of linear and weight growth (39). Zeiger and colleagues demonstrated that children who received the episodic use of high dose ICS (budesonide 1mg twice daily for 1 week) along with albuterol at the earliest recognition of patient-specific early signs of illness experienced comparable frequencies of exacerbations requiring OCS to those children who received daily low dose ICS (budesonide 0.5mg once daily for 12 months) (46).

A recent study including children 1-4 years of age with asthma symptoms on at least 7 out of 14 days during a run in period demonstrated that the “as needed” use of ICS (beclomethasone 800mcg) given when albuterol rescue was needed did not differ from daily ICS (beclomethasone 400mcg twice daily) in the time to first exacerbation requiring OCS (60).

Overall, these data indicate that the early episodic use of high dose ICS therapy, particularly in children as high risk for asthma (i.e. positive mAPI) may reduce the symptomatology during acute illnesses, and while the approach studied by Ducharme et al was effective in reducing exacerbations requiring OCS, the occurrence of growth effects may lessen the clinical appeal of this strategy. Recent demonstration the episodic high dose ICS was comparable to daily low dose ICS in terms of risk of exacerbation suggests that this approach may serve as an alternative strategy to daily therapy but remains associated with a reduced, but not zero, risk of exacerbation.
Summary Statement 8: For patients with mild-moderate asthma, consider recommending symptom-driven use of inhaled corticosteroids with concomitant inhaled beta-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 pre-defined medications as discussed above. However, if the yellow zone is reframed as a period of acute loss of asthma control, both intermittent as well as sustained temporary loss of control would be considered to be the yellow zone. Therefore, research evaluating intervention during very early signs of asthma worsening, as in “as needed” use of step-up medications along with rescue bronchodilator use, could be accepted as dynamic dosing, yellow zone strategy. Recently there have been results supporting this strategy.

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

Boushey et al utilized 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) (61). Adults (n=225) with EPR guideline–defined mild persistent asthma with well controlled asthma (low doses of ICS) were randomized to: a) low-dose ICS (200 mg twice daily) b) LTRA (20 mg of zafirlukast) or c) placebo. Subjects in all 3 groups instituted a symptom-based action plan when predetermined criteria suggesting lack of control was 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 their asthma symptoms worsened. The placebo group can therefore 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 prebronchodilator FEV1, bronchial reactivity, percentages of eosinophils in sputum, exhaled nitric oxide levels, scores for asthma control, and the number of symptom-free days but not in postbronchodilator FEV1 or quality of life. Based on these results, the authors suggest that it is possible to treat mild persistent asthma with short intermittent courses of inhaled or oral corticosteroids taken when symptoms worsen.
Three recent studies, two in adults and one in children, evaluated the novel approach of stepping down therapy in patients well controlled on low doses of ICS (EPR3 step 2 care) to 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 one of the trial arms enabling them to receive not only a bronchodilator, but also an antiinflammatory medication. In the BEST study, Papi et al examined 455 adult patients (18-65 years of age) with mild well-controlled asthma on 250 mg of beclomethasone twice daily (62). The patients were randomized to one of four groups: placebo bid + 250 μg of beclomethasone +prn albuterol (as needed combination Rx), placebo bid +albuterol prn (as-needed albuterol Rx), 250 μg beclomethasone bid + alb prn (regular beclomethasone Rx) and 250 μg beclomethasone +albuterol single inhaler bid + albuterol prn (regular combination Rx). They found that symptom-driven use of beclomethsone and albuterol in a single inhaler was as effective as regular use of beclomethasone bid regarding the primary outcome (AM peak flow). Notably, the number of exacerbations during the 6-month treatment was significantly lower in the as-needed combination therapy group (0.74) compared to the as-needed albuterol therapy group (1.63) but were 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 prn combination group; about ¼ the amount as daily Rx. This suggests that symptom-based use of ICS + 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, employing increased doses of ICS at the earliest signs of asthma worsening, was examined in 843 children 5-18 years of age in the TREXA trial (45). In this study, the ICS and albuterol were delivered in separate inhalers (as opposed to the above adult study in which both the ICS and albuterol were in a single inhaler). Participants who were well-controlled while receiving low dose beclomethasone were randomized to one of four 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 to the other three groups where ICS was used either as rescue or maintenance or both (28-35%). Interestingly, the secondary outcome, linear growth, was significantly worse in the combined and daily ICS arm compared to rescue ICS arm with growth being 1·1 cm (SD 0·3) less in the
combined and daily arms ($p<0.0001$), but not the rescue group ($p=0.26$). The rescue group also received
15-25% of the ICS dose that those in the combined and daily ICS groups received. The authors 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, multi-centered, RCT of 342 adults with mild to moderate controlled asthma assigned to one of three approaches of adjusting ICS therapy in adults with asthma (physician assessment--; biomarker- and symptom-based adjustment) (63). For symptom-based adjustment, ICS was taken with each albuterol rescue use, and for the other two arms the dose of ICS was adjusted every 6 weeks based upon measures of control. Similar to the results of the IMPACT and BEST trials regarding rescue ICS use with symptoms compared to other interventions in patients with mild and mild-moderate persistent asthma respectively, there were no significant differences in time to treatment failure.

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

**Dynamic Dosing Step-Up: Single Inhaler Maintenance and Reliever Therapy**

Multiple recent studies have consistently demonstrated efficacy of Single Inhaler Maintenance and Reliever Therapy (M&R) adjustment in the treatment of the yellow zone. Hence, this 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 that there is an FDA boxed warning regarding the use of the LABA component of this regimen.

A strategy termed adjustable maintenance dosing (AMD), using combination therapy with an ICS and a LABA, has been studied by a number of research groups. While the traditional fixed-dose strategy is designed to allow the patients to maintain complete control, the adjustable dosing strategy encourages the patient to escalate extra dosing based on symptoms. This may enable reduction in cumulative controller dose and avoidance of OCS.
Initial open-label studies suggested that patient-driven adjustable maintenance dosing (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 versus AMD doses in adults with persistent asthma came to a different conclusion. Fitzergald et al compared fixed dosing with fluticasone/salmeterol (250/50 mg twice daily) versus AMD with budesonide/formoterol (400/12 mg twice daily) (66). After a run-in period with each of these dosing strategies, subjects in the budesonide/formoterol arm halved their dose. They were then instructed to increase or decrease the numbers of puffs per day based on the following measures 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, subjects receiving stable dosing of 250/50 mg of fluticasone/salmeterol twice daily had significantly greater increases in symptom-free days, days free of rescue medication, and morning PEF. Notably, they also had experienced almost a halving of the exacerbation rate, compared with AMD with formoterol/budesonide. The authors 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.

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

The LABA formoterol is similar to SABA rescue medication in terms of rapidity of onset of bronchodilation. The possibility of using intermittent, symptom-based use of combination products with ICS and formoterol that can serve as both controller and reliever have been studied by numerous groups. The rationale of the maintenance and reliever dosing concept is that patients would need to possess a single inhaler both for maintenance and reliever therapy, thereby simplifying their regimen.

Furthermore, the ICS obtained with the additional doses might further reduce the risk of exacerbations. As seen in the Partridge study, when participants are faced with an exacerbation, most increase SABA immediately and delay their increase of ICS (Partridge, 2006). Maintenance and Reliever (M &R)
therapy therefore, may ensure prompt institution of anti-inflammatory therapy in addition to providing symptom relief. Additionally, a symptom-driven approach allows an acknowledgment 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 since it has been reported that many asthmatic patients 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, as symptom perception varies between people, a pure symptom-driven approach may not be feasible in a select sub-group (ie poor perceivers of dyspnea). Success of this strategy would therefore depend on effective provider-patient partnership and education including a written asthma action plan with instructions to increase their dose at early signs of acute loss of control.

The M&R strategy has been evaluated in multiple studies (72, 73) (74). In the STEAM study, patients with mild-to-moderate asthma received either M&R dosing with budesonide/formoterol or budesonide (double the maintenance dose used in the M&R arm) and as-needed SABA (72). After six months of treatment, patients in the SMART arm had significantly greater improvements in PEF from baseline compared with patients receiving budesonide and as-needed SABA (34.5 L/min vs. 9.5 L/min, P < 0.001). There was also a significantly reduced risk of severe exacerbations in the SMART arm (54%, P = 0.0011). The authors opined that this demonstrated that the M&R approach was superior at producing symptom relief with reduced overall medication dose.

The one-year STEP study evaluated the above two regimens in patients with a greater severity of asthma (83% severe) (74). The time to first severe exacerbation (hospitalization/emergency room treatment or systemic steroids due to asthma worsening or a fall in morning PEF to ≤70% of baseline on two consecutive days) was prolonged in the M&R arm compared with the budesonide arm (P<0.001) and the risk of having a severe exacerbation was 39% lower (P<0.001). The M&R group had 45% fewer severe exacerbations requiring medical intervention per patient compared with the budesonide group (P<0.001) and the mean daily ICS dose was lower in the M&R group than in the budesonide group (466 mcg/day vs. 640 mcg/day).
The one-year STAY study compared three different regimens in children and adults with moderate asthma: budesonide plus as-needed SABA (terbutaline); budesonide/formoterol plus as-needed SABA; and SMART budesonide/ formoterol (73). This multicenter clinical trial involved 2760 patients with asthma aged 4 to 80 years (FEV1 60% to 100% of predicted value). The results suggested that M&R dosing (mean daily budesonide dose of 240 μg per day in adults and 126 μg in children) significantly prolonged the time to first severe exacerbation compared with the other two regimens (P<0.001). All treatments improved asthma symptoms as measured by reduced need for reliever medication and reduced nights with awakenings. Budesonide/formoterol SMART 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 SMART regimen also prolonged the time to the second, and third exacerbations requiring medical intervention, reduced severe exacerbation rates, and improved symptoms, awakenings, and lung function compared with both fixed-dosing regimens. The observation was made that the timing of the increased ICS dose (SMART) was likely the key factor that contributed to the improved outcomes compared to the magnitude of the increase in the budesonide dose (fourfold).

The SMILE trial attempted to characterize the contribution of budesonide and formoterol as reliever therapy (75) All patients in this one-year study received budesonide/ formoterol (one inhalation twice daily) as maintenance treatment, but were randomized to receive one of three different as-needed reliever regimens: additional inhalations with budesonide/ formoterol, formoterol alone, or terbutaline alone. As in earlier studies, the time to first severe exacerbation was significantly increased in the M&R arm compared with the other two strategies (P = 0.0048 vs. formoterol relief and P<0.0001 for terbutaline relief) and the yearly exacerbation rate was decreased by 33 and 48%, respectively. However, the M&R strategy failed to improve the percentage of asthma control days or patient-reported quality of life suggesting as-needed budesonide/formoterol may have a greater role in mitigating exacerbations than on every-day asthma control.

COMPASS was a six-month, double-blind study that compared a budesonide/formoterol M&R with fluticasone/salmeterol or budesonide/ 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 SMART regimen (P = 0.0034 compared with fluticasone/salmeterol, and P = 0.023 compared with budesonide/formoterol) and
patients had 28-39% fewer exacerbations, all treatments used in the study produced similar improvements in lung function and asthma control days. There was also no difference between the three treatments in the rate of mild exacerbations or in patient-reported quality of life. Mean daily doses of ICS were lowest in the SMART arm (755 μg per day BDP equivalent compared with 1000 μg per day in the other two arms) highlighting the ability of the SMART regimen to achieve a lower effective dose of ICS.

COSMOS was a one-year, open-label comparison of AMD with fluticasone/salmeterol plus salbutamol as needed, and SMART with budesonide/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 to the AMD group, SMART treatment with budesonide/formoterol significantly reduced risk and rate of exacerbations (instantaneous risk reduced by 25%; exacerbation rate reduced by 22%). The ICS dose was similar in both arms of the study (1420 μg daily BDP equivalent for budesonide and 1402 μg for fluticasone), but patients in the SMART arm had significantly reduced as-needed medication use and increased odds of having low weekly levels of rescue medication use. Interestingly, there was no difference in patient reported quality of life between the two groups.

In a recent 24-week trial undertaken at four primary health-care practices and one hospital in New Zealand, patients (aged 16—65 years) with a recent asthma exacerbation were randomly assigned to M & R strategy (2 actuations of budesonide—formoterol (200 mcg/6 mcg bid with one additional actuation as needed) or standard fixed-dose regimen (1-2 actuations of salbutamol as needed in addition to maintenance bud/form bid) (78). MDIs were monitored electronically to measure actual use of medication. The primary outcome was the proportion of participants with at least one high-use episode of β agonist (more than eight actuations per day of bud—form in addition to the four maintenance doses in the M&R group or more than 16 actuations per day of salbutamol in the standard). No significant difference was noted between the M & R (n=151) and standard groups (n=152) in the proportion of participants with at least one high-use episode of β agonist; there were fewer days of high use in the M&R group (mean 5.1 days [SD 14.3] vs 8.9 days [20.9] p=0.001]). Of the patients who had at least one high-use episode, those in the M&R group had fewer days of high use without medical review (8.5 days [17.8] vs 18.3 days [24.8] p=0.001). Participants in the M&R group had fewer severe asthma exacerbations (35 vs 66 p=0.004).

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 federal regulatory approval of this strategy. These, and similar protocols, are being used in Europe. Given the safety and efficacy of the M&R approach as reflected in the data in this document, this approach may be considered an option for use in the Yellow Zone.

The concerns of the FDA stemmed from a review of three prospective, randomized, placebo-controlled, double-blind clinical studies of formoterol at dosages of 12 mcg and 24 mcg bid for the treatment of patients with asthma (80). In their review, they found that a greater number of patients treated regularly with formoterol 24 mcg bid 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 formoterol 24 mcg bid for 12 weeks, had a serious asthma exacerbation compared to none of 136 placebo-treated patients. In the second study, 5 of 136 patients (3.7%) treated with formoterol 24 mcg bid for 12 weeks, had a serious asthma exacerbation compared to 2 of 141 placebo-treated patients (1.4%). In the third study, 11 of 171 pediatric patients (6.4%) treated with formoterol 24 mcg bid for 12 months, had a serious asthma exacerbation compared to none of 176 placebo-treated patients. In the two 12-week studies in adults/adolescents, the serious asthma exacerbation events occurred between 10 days and 2.5 months after the initiation of treatment. In the 1-year pediatric study, the serious but nonfatal asthma exacerbations occurred between day 50 and day 297 of treatment.

In the studies exploring the dynamic dosing concept (M & R strategy using budesonide-formoterol), the study protocols typically permitted a maximum of 10 as needed inhalations and 7 or children in a single day (in addition to their daily maintenance treatment) before contacting the investigator. In the pediatric study by Bisgaard (n=106) fewer than 5% of patients in the study took this maximum dose and there were no SAEs. (81)

In the study by O’Byrne (73), 2,760 patients with asthma aged 4–80 years (FEV1 60–100% predicted received either terbutaline 0.4 mg as SABA with budesonide/formoterol 80/4.5 mcg twice a day or budesonide 320 mcg twice a day or budesonide/formoterol 80/4.5 mcg twice a day with 80/4.5 mcg as-needed (budesonide/ formoterol M& R). Children used a once-nighturnal maintenance dose. There were 495 episodes with an increase in as-needed medication to more than four inhalations per day.
over the baseline value in the M & R group, of which 37 were associated with an exacerbation; 1,347 episodes in the bud/form_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 eight inhalations per day above baseline in the M&R, bud/form_SABA, and bud_SABA groups, respectively; of these, only 2 preceded an exacerbation in the M&R 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 reliever use free in M&R group. The mean number of as needed doses of bud/form was one additional dose per day consistent with other studies (i.e., 50% of days with use of an average extra one inhalation per day). In addition, there were notably fewer episodes of high as-needed medication use (at least eight inhalations above baseline), in the M & R group compared with the fixed dosing groups. M & R was also associated with only 2 severe exacerbations in the high-user subgroup compared with 17–23 severe exacerbations in as needed SABA group. The average daily dose of budesonide resulting from M &R use was 80 mcg higher than for patients who used 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 the study in New Zealand by Patel and colleagues, the M &R regimen resulted in higher ICS exposure (943.5 μg budesonide per day [1502.5] vs 684.3 μg budesonide per day [390.5], respectively; ratio of means 1.22 [1.06—1.41]; p=0.006), but reduced oral corticosteroid exposure (77.5 mg prednisone [240.5] vs 126.6 mg prednisone [382.1], respectively; p=0.011), with no significant difference in composite systemic corticosteroid exposure (793.7 mg prednisone equivalent per year [893.1] vs 772.1 mg prednisone equivalent per year [1062.7], respectively; 1.03 [0.86—1.22]; p=0.76). (78).

A recent updated 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 RCTs in adults, there were a total of 20 RCTs with over 10,000 adults and seven RCTs with 2788 children. They found that, in adults, there were significantly fewer asthma-related SAEs in those taking regular formoterol and ICS compared with ICS alone, and no significant difference in all-cause SAEs. 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 over 13,000 people, one
related to asthma. The authors summarize that no conclusions can be drawn about possible differences in
the risk of death relating to taking ICS alone or with formoterol. Currently there are several
large clinical trials (adults, adolescents, children) in the USA examining the risks of ICS+LABA
combination compared to 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 + anticholinergics, and leukotriene
modifiers. However, these options may be considered in individual cases at the discretion of the
provider.

Single high dose of ICS

Since one of the potential concerns is the systemic effects of high dose oral steroids, use of one large
dose of inhaled steroids might help minimize some of the side effects. In a study of mild asthma
exacerbations, 19 patients were randomized to either doubling the dose of ICS or adding a single dose of
3200 ug budesonide (83). Those receiving the high single dose treatment initially showed a greater
increase in PEF in the first week (87.4 (4.7) l/min v 76.7 (5.3) l/min, p=0.029). However, at 3 weeks
there was no difference between the groups.

SABA + anticholinergics:

There is controversy over the use of anticholinergic agents, such as ipratropium, as a rescue
bronchodilator in the care of patients with acute asthma. While bronchodilation has been demonstrated
via blockade of resting cholinergic bronchomotor tone and inhibition of cholinergic bronchoconstriction,
data suggests these anticholinergic agents provide less bronchodilation and slower onset of action than
short acting β-agonists. (84) (85)

Studies examining the combined use of β2-agonists plus ipratropium have shown variable results. A
randomized study by Rebuck and colleagues found the greatest improvement in FEV1 occurred at 45
and 90 minutes after therapy with the combined use of ipratropium and fenoterol, compared to either alone in 148 patients with asthma with acute exacerbations (86). On the other hand, Karpel and associates demonstrated no long-term benefit with combination therapy in patients with acute asthma in the ED setting. Though patients receiving the combination of albuterol plus ipratropium demonstrated greater improvement in FEV1 at 45 minutes, no sustained benefit was seen at 90 minutes compared to either of the agents alone (87). It should be noted that in most of these studies, a low-dose of ipratropium was used.

Rodrigo and Rodrigo reported added efficacy with high-dose 4 puffs of ipratropium therapy (21 mcg per puff) along with albuterol (120 mcg per puff) in one inhaler, every 10 minutes for 3 hours (88). In this study of 180 patients with an acute asthma exacerbation (i.e. red zone exacerbation), those who received combination therapy had greater improvements in PEF (20.5%) and FEV1 (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 FEV1 of 30% or less of predicted and symptoms for 24 hours or more before ED presentation.

**Montelukast**

Three studies have examined the potential role of intermittent montelukast therapy in young children with overall modest results. Robertson et al studied children 2-14 years of age with intermittent asthma and found that montelukast started at the onset of URI or asthma symptoms and continued for at least 7 days resulted in modest reductions in health care utilization and symptom severity but no effect on OCS use, episode duration or SABA use (37). Bacharier et al found that starting montelukast along with albuterol at the earliest recognition of patient-specific early signs of illness in children 1-5 years of age with severe intermittent wheezing also did not reduce OCS use but did lessen symptom severity during episodes relative to use of albuterol alone (36). Valovirta and colleagues compared daily and episodic montelukast (treatment started with signs/symptoms consistent with an imminent cold or breathing problem) to placebo in children 6 months to 5 years of age with episodic wheezing and found no difference between either montelukast arm and placebo in the number of episodes culminating in an asthma attack over the 1 year study (89).
**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 as well as adults. When designing these studies, investigators should consider the potential impact of the dose, timing and frequency of escalation of the intervention, as well as the population being studied. Also imperative is the need for ongoing research to define robust early predictors of asthma exacerbation.
1129 FIGURES

1130
Figure 1

1131
Asthma Severity (Step): (Step) Asthma Control: ACT / CACT Score:

**Quick Reliever Medicine** *Use as Needed in all Zones*
- Albuterol 90 mcg inhale 2 puffs every 4 hours as needed
- Albuterol 0.083% Neb Solution inhale 1 dose by nebulizer every 4 hours as needed

**Green Zone/Daily Plan**
This is the feeling good zone, where you should be everyday.
1. Cough, wheeze or Quick Reliever use 2 or less days/week
2. Sleep or usual activities without cough or wheeze

**MEDICATION**

**What to do for an Asthma Episode**
If the following happens:

**Step-up therapy if the following occur:**
1. An increase in Cough, wheeze, or other asthma symptoms
2. An increase is the use of Quick Reliever (albuterol)
3. Cough or wheeze during sleep or with usual activities
4. A decline in Peak flow rate of 15% (number) or more
5. If Peak flow <80% of personal best (number) after use of a Quick Reliever (albuterol)
6. Exposure to a known trigger (respiratory tract infection) or allergen

Next:
1. Use 2-4 puffs of your Quick Reliever medication albuterol (or 1 nebulized albuterol 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 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**

**Options for step-up therapy:**

<table>
<thead>
<tr>
<th>Scheduled Dosing Step-Up</th>
<th>Dynamic Dosing Step-up</th>
<th>M&amp;R step-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase total ICS dose in 24 hours</td>
<td>ICS along with rescue SABA use (use of concomitant dose of ICS with each SABA dose)</td>
<td>ICS-Formoterol-Maintenance and Reliever Therapy</td>
</tr>
</tbody>
</table>
Red Zone - systemic steroids

This is when an asthma trigger is causing any of the following:

1. Cough or wheeze throughout the day
2. Short of breath at rest or with talking or walking
3. Chest is sinking in around the ribs or at the neck
4. Quick Reliever use several times/day

Step up to this medicine and continue Yellow Zone medicine

Oral steroids

*Call the provider at (___)________ or call the provider triage line at or seek medical attention
*Call 911 if lips or fingernails are blue

Figure 2

May switch among options
**Titles for Figures:**

1186  Figure 1: Yellow Zone: The zone of acute loss of asthma control.

1187  Figure 2: Sample Asthma Action Plan
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