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Treatment Strategies for the Yellow Zone

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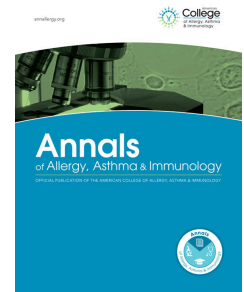
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Abbreviations/Acronyms:

Asthma Control Questionnaire, ACQ

confidence interval, CI

emergency department, ED

exhaled nitric oxide, eNO

forced expiratory volume in the first second, FEV1

Global Initiative for Asthma, GINA

hazard ratio, HR

inhaled corticosteroid, ICS

leukotriene receptor antagonist, LTRA

long-acting beta-agonist, LABA

maintenance and reliever, M+R

number needed to treat, NNT

odds ratio, OR

oral corticosteroids, OCS

peak expiratory flow rate, PEFr

red zone, RZ

risk differences, RD

respiratory tract infections, RTI

risk ratio, RR

short-acting beta-agonist, SABA

single maintenance and reliever therapy, SMART

yellow zone, YZ

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1 Introduction

2 Asthma control changes over time and many factors contribute to this variability.
3 Environmental exposures such as seasonal allergen fluctuations, second-hand tobacco exposure,
4 and viral upper respiratory tract infections (RTI) are just a few of the known triggers of lability¹.
5 In addition, host factors such as inhaler technique and co-morbid conditions including atopic
6 diseases, obesity, and acid reflux can also contribute to this changeability. During times of
7 lability, overzealous intervention can lead to overuse of oral corticosteroids (OCS) and
8 healthcare visits, while delayed treatment can lead to severe exacerbation, with potential
9 hospitalization, or even death.

10 To help recognize and respond to changes in control, guidelines recommend that
11 clinicians provide patients with a written asthma action plan². Typically, such plans follow a
12 "traffic light" model and provide written directions regarding treatment recommendations when
13 asthma is stable (green zone), when asthma deterioration is detected and requires intervention in
14 an attempt to prevent further escalation (yellow zone [YZ]), and when an exacerbation is
15 occurring, requiring systemic corticosteroids and/or urgent medical care (red zone [RZ]). Of
16 particular importance is the early recognition when reaching the YZ, as early identification and
17 aggressive intervention may reduce the chances of further deterioration into the RZ.

19 Identifying the Yellow Zone

20 Making recommendations regarding YZ therapy remains difficult, as there is no single
21 reliable predictor for asthma exacerbation. Diagnosing patients within the YZ requires a
22 combination of clinical markers of asthma severity and control. An increase in asthma symptoms
23 (≥ 2 times per day) greater than baseline, increased use of rescue medications, increase in

nocturnal symptoms, and a decrease in peak expiratory flow (PEF) are all possible signs of impending exacerbation²⁻⁴. Likely, no one marker is adequate, but perhaps using a combination of the above measures may aid in the timely and appropriate identification of an impending exacerbation.

Time Frame of an Asthma Exacerbation

Upon loss of control, the timing of escalation and de-escalation of a patient's asthma regimen is crucial in management. In the Pediatric Asthma Control Trial (PACT), children showed changes in cough and wheeze scores, albuterol rescue use, and PEF from three to 12 days before an exacerbation⁵. Regardless of treatment, outcome measures of symptoms and albuterol rescue use did not return to baseline until at least 10 days after the start of loss of control and PEF changes, and often remained abnormal for even longer periods. Additionally, the International Asthma Patient Insight Research (INSPIRE) study report mean length of time to peak symptoms worsening was 5.1 days⁶. Taken together, these studies support early escalation upon the first sign of loss of control and should be continued for at least 10 days².

Strategies Proposed for Treatment of Patients Who Are in the Yellow Zone

Multiple strategies have been proposed for the treatment of patients who enter the YZ (Table 1). These include regimens that involve the use or escalation of doses of ICS, while others do not (scheduled SABA and intermittent use of a leukotriene receptor antagonist [LTRA]).

Some argue that initiation or escalation of ICS even at the first sign of an exacerbation makes no sense, as they take two to six weeks to exert maximal benefit, but Gibson et al. found that even a single dose of inhaled budesonide (2,400 µg) demonstrated beneficial effects on

airway inflammation and hyperresponsiveness in as early as six hours after dosing⁷. This suggests that there may be an acute anti-inflammatory effect from ICS. Furthermore, Szefer et al. found statistically significant improvements in PEF, symptom scores, and rescue albuterol use beginning on day 1 of treatment with fluticasone propionate (25 µg to 500 µg twice daily)⁸. Taken together, these findings do provide a rationale for escalation of ICS dose as a strategy for YZ treatment.

Scheduled SABA

In the United States, the National Asthma Education and Prevention Program Third *Expert Panel (EPR3)* recommends temporarily scheduling SABA every 3-4 hours for 24-48 hours when in the YZ⁹. However, no evidence supports this recommendation. While this strategy may provide temporary symptom relief and increase forced expiratory volume in the first second (FEV1), it is unlikely that it can prevent progression into the RZ, as the SABA would not be expected to reduce the airway inflammation causing the exacerbation. With this in mind, the 2019 Global Initiative for Asthma (GINA) guidelines no longer recommends treatment with SABA alone, noting that this strategy does not prevent severe exacerbations¹⁰.

Intermittent Leukotriene Receptor Antagonist

The PRE-EMPT study found that introduction of montelukast at the first sign of an exacerbation in children with intermittent asthma resulted in reduction in health care utilization (by 28.5%), asthma symptoms, as well as school and parental work absence. However, it did not result in reduction of beta-agonist or OCS use¹¹.

Similarly, the Acute Intervention Management Strategies (AIMS) trial found that in children with intermittent wheezing, episodic use of montelukast (when added to albuterol therapy) early in RTIs led to reduction in trouble breathing (37% [P=0.003]) and interference with activity scores (40% [P=0.001])¹². These findings were most evident in children with positive asthma predictive indices. However, this strategy did not increase the proportion of episode-free days or decrease OCS use.

Meanwhile, the Wheeze and Intermittent Treatment (WAIT) trial found no difference between intermittent montelukast and placebo in terms of unscheduled medical visits for wheezing episodes¹³.

Additionally, Valovirta et al. found no significant difference between daily or episode-driven montelukast use in the number of asthma episodes culminating in an exacerbation compared to placebo in children 6 months to 5 years old¹⁴. However, beta-agonist use was reduced with both daily (P=0.048) and intermittent montelukast treatment (P=0.028) compared with placebo.

Thus, studies have shown some benefit in the acute use of a LTRA as a YZ medication, but overall did not demonstrate a decrease in exacerbation rate. Moreover, such studies have only been undertaken in the pediatric population.

Intermittent ICS Dosing

In 2016, a meta-analysis found that when compared to placebo, pre-emptive high-dose intermittent ICS reduced risk of exacerbation by 35% in preschool-age children with intermittent asthma or viral-triggered wheezing (5 studies, N=422; RR 0.65; 95% confidence interval [CI], 0.51–0.81, p=0.0002, NNT=6)¹⁵. The corticosteroid regimens used in these studies were

nebulized budesonide 1 mg twice daily, inhaled beclomethasone (1500 µg), inhaled budesonide (1200 to 3200 µg), or inhaled fluticasone (1500 µg) daily. The children in these studies were started on high-dose ICS at the first sign of an upper RTI and continued on this regimen for seven to 10 days. Overall, there is strong evidence to support intermittent high-dose ICS for preventing exacerbations in this specific pediatric population¹⁶, and as a result is recommended in the 2018 GINA guidelines¹⁷.

As for school-aged children and adults, a 2015 Cochrane Review identified two studies demonstrating that use of intermittent ICS at the start of an asthma episode reduced the risk of requiring OCS in older children [OR 0.57; 95% CI, 0.29-1.12) and adults [OR 0.10; 95% CI, 0.01-1.95), and one study demonstrating improvement in lung function in adults¹⁸. However, overall, the strength of evidence was deemed to be of low quality due to the paucity of published data.

Short-Term Increase in Scheduled ICS Controller (Double, Quadruple, Quintuple)

Doubling Maintenance ICS Dose

Initially, many action plans advocated doubling the dose of ICS in the YZ as several studies had previously demonstrated efficacy with this strategy. However, more recent studies in both children and adults could not replicate this effect.

Harrison et al. found no effect with this strategy on the number of patients needing prednisolone, lowest PEF recorded, increase in symptom scores, highest symptom score recorded, or time to recovery for PEF and symptom scores¹⁹. Similarly, Fitzgerald et al. found no difference in terms of treatment failures: requiring systemic corticosteroids, unscheduled visit to a physician, and asthma returning to baseline²⁰. Next, Garrett et al. found no significant

difference in PEFs, diurnal peak flow variability, or symptom scores two weeks following an exacerbation²¹. Additionally, Rice-Mcdonald et al. found no difference in terms of treatment failures or median PEF (as percentage of run-in best)²². Finally, a 2016 Cochrane Review of patients with mild to moderate asthma found that the odds of needing OCS or having an unscheduled physician visit or acute care visit were not significantly reduced among patients who doubled their ICS²³.

Quadrupling Maintenance ICS Dose

Looking at a more substantial increase in ICS dose, Osborne et al. found that quadrupling ICS dose (in patients ≥ 16 years old) upon loss of asthma control resulted in fewer patients requiring OCS compared with placebo: 12 of 56 (21%) in the quadrupling group versus 19 of 38 (50%) in the placebo group (RR=0.43 [95% CI, 0.24–0.78, P=0.004])²⁴.

Similarly, in the Four-Fold Asthma Study (FAST) (a pragmatically designed trial involving patients ≥ 16 years old on maintenance ICS), McKeever et al. found that temporary quadrupling of ICS dose upon deterioration of asthma control resulted in significantly fewer severe exacerbations (defined as requiring systemic glucocorticoids or an unscheduled health care consultation): 45% in the quadrupling group versus 52% in the maintenance group, with an adjusted hazard ratio (HR) for the time to a first severe exacerbation of 0.81 (95% CI, 0.71-0.92; P=0.002; NNT=15)²⁵.

Quintupling Maintenance ICS Dose

In contrast to the quadrupled ICS dose studies, Jackson et al. did not find the same benefit with an even higher ICS dose (quintupled) in children (ages 5-11 years old) with mild to

moderate asthma²⁶. Children were treated with daily low dose ICS (fluticasone propionate 88 µg twice daily) and were randomly assigned to either continue the same dose (low-dose group) or use a quintupled dose (high-dose group; fluticasone 440 µg twice daily) for seven days at the early signs of asthma deterioration. Results showed no significant difference in rate of severe exacerbations requiring systemic glucocorticoids between the two groups (0.48 exacerbations per year in the high-dose group versus 0.37 in the low-dose group; risk ratio [RR], 1.3; 95% CI, 0.8-2.1; P=0.30). Moreover, no significant difference was found between the two groups regarding time to first exacerbation, rate of treatment failure, symptom scores, and albuterol use during YZ episodes. Of note, there was a decrease in linear growth in the high-dose group (between group difference of -0.23 cm per year [P=0.06]), which may be due to the increased total glucocorticoid exposure in this group (16% higher).

When comparing these two recent trials, the study by Jackson et al. had fewer than expected exacerbations, with lack of efficacy seen following escalation of dose, while in the pragmatically designed study by McKeever et al. approximately 50% of subjects had an exacerbation and efficacy was seen with ICS dose escalation. A possible reason for this discrepancy is adherence to maintenance ICS. Exclusion of patients with poor adherence by Jackson et al. may have resulted in the overall reduction in exacerbation rates that they observed. For such patients with good maintenance ICS adherence, quadrupling the ICS dose may not be the answer due to ICS's flat dose response; that is, it plateaus with no further therapeutic response with increasing dose of the ICS²⁷. Unfortunately, in the real world, adherence is a problem as few patients are truly adherent to their maintenance medication. Often, only when faced with loss of asthma control do patients begin to comply with their controller therapy, while

161 increasing their rescue inhaler use as well. Likely, patients who essentially transition from non-
162 adherence to adherence with ICS (albeit temporarily) are the ones experiencing the benefit of
163 protection against exacerbations. Furthermore, ICS efficacy may improve with increased dosing
164 frequency²⁸; that is, twice daily dosing is more effective than the same total dose of ICS dosed
165 once daily. Putting this all together, the correct recommendation to patients may be to utilize an
166 approach where ICS dosing is tethered to reliever beta-agonist use as this may ultimately achieve
167 frequent ICS dosing.

169 **Dynamic Dosing Method One: Symptom-Driven Use of ICS with SABA**

170 In the beclomethasone plus salbutamol (also known as albuterol) (BEST) study, adult
171 patients with mild asthma were assigned to receive one of four inhaled treatments: placebo twice
172 daily plus 250 µg of beclomethasone and albuterol in a single inhaler as needed (as-needed
173 combination therapy); placebo twice daily plus albuterol as needed (as-needed albuterol
174 therapy); 250 µg of beclomethasone twice daily and albuterol as needed (regular beclomethasone
175 therapy); or 250 µg of beclomethasone and albuterol in a single inhaler twice daily plus albuterol
176 as needed (regular combination therapy)²⁹. Symptom-driven use of inhaled beclomethasone (250
177 µg) and albuterol in a single inhaler was found to be as effective as regular use of inhaled
178 beclomethasone (250 µg twice daily). Morning PEF measures during the last two weeks of the 6-
179 month treatment were higher ($P=0.04$) and the number of exacerbations during the 6-month
180 treatment were lower ($P=0.002$) in the as-needed combination therapy group compared to the as-
181 needed albuterol therapy group. However, neither the PEF nor the number of exacerbations were
182 significantly different from those in the groups receiving regular beclomethasone therapy or
183 regular combination therapy. Importantly, the cumulative dose of inhaled beclomethasone was

significantly lower in the as-needed combination therapy group than in the groups receiving regular beclomethasone therapy or regular combination therapy (18.48 vs 76.97 $P < 0.001$ for both comparisons).

Next, the Best Adjustment Strategy for Asthma in the Long Term (BASALT) study assessed whether a lower dose of beclomethasone would produce similar results³⁰. Patients with mild to moderate asthma controlled with beclomethasone 40 μg two puffs twice daily were randomized to either scheduled beclomethasone or on-demand beclomethasone with each albuterol use. The treatment failure rate did not differ between the two groups. However, total monthly ICS dose was significantly lower in the on-demand group (832 μg vs. 1610 μg , $p = 0.01$).

Meanwhile, in the Treating Children to Prevent Exacerbations of Asthma (TREXA) study, patients (ages 5-18 years old) with mild persistent asthma who were well-controlled on low dose beclomethasone (40 μg twice daily) 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); or twice daily placebo with placebo plus albuterol as rescue (placebo group)³¹. The frequency of exacerbations was found to be significantly higher in the placebo group (49%) compared to the other three groups: daily (28%, $p = 0.03$), combined (31%, $p = 0.07$), and rescue (35%, $p = 0.07$). As for frequency of treatment failure, this was 23% in the placebo group, compared with 5.6% in the combined ($p = 0.012$), 2.8% in the daily ($p = 0.009$), and 8.5% in the rescue ($p = 0.024$) groups. Compared to the placebo group, linear growth was significantly diminished in the combined and daily ICS arms with growth being 1.1 cm less in these two arms

($p < 0.0001$) but not in the rescue group ($p = 0.26$). The rescue group also received 15-25% of the ICS dose compared to those in the combined and daily ICS groups.

Dynamic Dosing Method Two: Single Maintenance and Reliever Therapy (SMART)

The strategy of using a combination of ICS and long-acting beta-agonist (LABA) as a controller and quick reliever (termed *single maintenance and reliever therapy* [SMART]) has also been investigated as a potential therapeutic regimen for the management of persistent asthma.

Rabe et al. compared budesonide/formoterol (a rapid onset LABA) in a single inhaler (used for both maintenance and symptom relief therapy) with a higher dose of budesonide plus as-needed terbutaline³². Included in the study were patients (ages 11-79 years old) with mild-to-moderate asthma on daily ICS. Participants were randomized to either budesonide/formoterol (80/4.5 µg, two inhalations daily) for maintenance plus additional inhalations as needed for symptom relief or budesonide (320 µg daily) for maintenance and terbutaline as needed for symptom relief. The budesonide/formoterol group had greater improvements in morning PEF compared to the budesonide group (increases of 34.5 L/min vs 9.5 L/min, respectively; $p = < 0.001$). Moreover, risk of having a severe exacerbation (hospitalization/ED treatment, OCS, or a $> 30\%$ decrease from baseline in morning PEF on 2 consecutive days) was 54% lower with budesonide/formoterol vs budesonide ($p = 0.0011$). The budesonide/formoterol group had 90% fewer hospitalizations/ED treatments compared to the budesonide group (1 vs 10, respectively; $p = 0.026$). Of note, the budesonide/formoterol group experienced this increased efficacy with less ICS compared to the budesonide group (240 µg/d vs 320 µg/d, respectively). Furthermore, the

budesonide/formoterol group had 77% fewer OCS treatment days compared to the budesonide group (114 days vs 498 days, respectively).

Next, in a study of children (ages 4-11 years old) with asthma uncontrolled on ICS, Bisgaard et al. investigated whether using budesonide/formoterol for maintenance and reliever therapy could reduce exacerbations³³. The participants were randomized to one of three arms: budesonide/formoterol 80/4.5 µg daily maintenance plus additional inhalations for symptom relief (SMART group); budesonide/formoterol 80/4.5 µg daily for maintenance plus terbutaline as needed for symptom relief (fixed combination group); or higher-dose budesonide 320 µg daily plus terbutaline as needed for symptom relief (fixed-dose budesonide group)³³. Time to first exacerbation was found to be prolonged in the SMART group compared to the fixed-dose budesonide ($p=0.02$) and fixed-dose combination ($p < 0.001$) groups. Next, rate of exacerbation requiring medical intervention was reduced by 70 to 79% with SMART versus fixed-dose budesonide and fixed-dose combination (0.08/patient vs 0.28/patient and 0.40/patient, respectively; both $p<0.001$). Moreover, mild exacerbation days and nocturnal awakenings were significantly lower with SMART. Furthermore, yearly growth among the patients in the SMART group improved by one centimeter compared to the fixed-dose budesonide group ($p<0.01$).

Additionally, in a study by Papi et al., patients (≥ 18 years old), who at the time were being treated with beclomethasone/formoterol 100/6 µg twice daily, were randomly assigned to receive as their reliever medication either beclomethasone/formoterol 100/6 µg or salbutamol³⁴. The beclomethasone/formoterol maintenance and reliever (M+R) treatment group was found to exhibit significantly increased time to first exacerbation compared to the beclomethasone/formoterol and SABA rescue group (209 days vs 134 days), with a 36% reduction in risk of severe exacerbation (defined as requiring hospital admission, ED visit, or use

of systemic corticosteroids for ≥ 3 days) (HR 0.64 [95% CI, 0.49-0.82]; $p=0.0005$). In addition, the number of days with mild exacerbations was also lower in the M+R group than with the salbutamol as needed group (56.04 vs 65.11 days per patient per year; 0.86 [0.76-0.98]; $p=0.021$).

A systematic review and meta-analysis, that included 16 randomized clinical trials (n=22,748 patients), found that among patients ≥ 12 years old (n=22,524), SMART was associated with a reduced risk of exacerbations compared with the same dose of ICS and LABA as the controller therapy (RR, 0.68 [95% CI, 0.58-0.80]; risk differences [RD], -6.4% [95% CI, -10.2% to -2.6%]) and a higher dose of ICS and LABA as the controller therapy (RR, 0.77 [95% CI, 0.60-0.98]; RD, -2.8% [95% CI, -5.2% to -0.3%])³⁵. When compared with ICS alone as the controller, similar findings were observed. As for younger patients (ages 4-11 years old), evidence was limited (n=341); however, SMART was also associated with a reduced risk of exacerbations compared with a higher dose of ICS as the controller therapy (RR, 0.55 [95% CI, 0.32-0.94]; RD, -12.0% [95% CI, -22.5% to -1.5%]) or the same dose of ICS and LABA as the controller therapy (RR, 0.38 [95% CI, 0.23-0.63]; RD, -23.2% [95% CI, -33.6% to -12.1%]). The investigators concluded that SMART was associated with a lower risk of exacerbations compared with ICS as the controller therapy (with or without a LABA) and SABA as the reliever.

More recently, Bateman et al. conducted a trial in which patients (≥ 12 years old) with mild asthma were randomly assigned to either twice-daily placebo plus budesonide/formoterol (200/6 μg) used as needed for symptom relief or budesonide maintenance therapy (200 μg twice daily) plus terbutaline used as rescue therapy³⁶. They found that budesonide/formoterol used as needed was non-inferior to budesonide maintenance therapy with regard to the annualized rate of

severe exacerbations (0.11 and 0.12, respectively). Moreover, time to first exacerbation was similar between the two groups; however, budesonide/formoterol used as needed was inferior in controlling symptoms based on Asthma Control Questionnaire (ACQ)-5 scores. As for daily ICS exposure, patients in the budesonide/formoterol as needed group had approximately a quarter of the dose compared to those in the budesonide maintenance group (66 µg vs. 267 µg, respectively).

In another recent study by Obyrne et al., patients (≥ 12 years old) with mild asthma were assigned to one of three arms: twice-daily placebo plus terbutaline used as needed (terbutaline group); twice-daily placebo plus budesonide/formoterol (200/6 µg) used as needed (budesonide/formoterol group); or twice-daily budesonide (200 µg) plus terbutaline used as needed (budesonide maintenance group)³⁷. With regard to percentage of weeks with well-controlled asthma, budesonide/formoterol was superior to terbutaline (34.4% vs. 31.1% of weeks; OR, 1.14; 95% CI, 1.00-1.30; $P=0.046$), but inferior to budesonide maintenance therapy (34.4% and 44.4%, respectively; OR, 0.64; 95% CI, 0.57-0.73). With regard to the annual rate of severe exacerbations, this was 0.20 with terbutaline, 0.07 with budesonide/formoterol, and 0.09 with budesonide maintenance therapy; the rate ratio was 0.36 (95% CI, 0.27-0.49) for budesonide/formoterol versus terbutaline and 0.83 (95% CI, 0.59-1.16) for budesonide/formoterol versus budesonide maintenance therapy. Thus, in the case of symptom control, as-needed budesonide/formoterol was superior to as-needed terbutaline, but was inferior to maintenance budesonide therapy. However, exacerbation rates were similar in both the budesonide maintenance and budesonide/formoterol groups, and lower compared to terbutaline. Furthermore, budesonide/formoterol as needed resulted in substantially lower daily glucocorticoid exposure compared with budesonide maintenance therapy (57 µg vs 340 µg).

Overall, the above data indicate the utility of dynamic dosing; a strategy that is simple, empowers patients, and likely reflects what patients do in real life. Importantly, the strategy of symptom-driven ICS in tandem with rescue beta-agonist use (whether short or long acting) seems to result in a decrease in exacerbations, while minimizing ICS exposure. In fact, as a Step 1 controller for all patients ≥ 12 years old, the 2019 GINA guidelines now recommend as-needed low dose ICS-formoterol (also an option as a Step 2 controller) or low dose ICS taken whenever a SABA is taken (also an option as a Step 1 controller for children 6-11 years old)¹⁰. In addition, as-needed low dose ICS-formoterol is now the preferred reliever therapy for all Steps of asthma care. These new recommendations, therefore, reinforce the robust data for this approach of rescue therapy tethered to anti-inflammatory ICS.

Conclusion

In summary, presently multiple YZ strategies exist, but only a few have been shown consistently effective. Scheduled SABA provides temporary symptom relief, but no specific evidence suggests it can prevent progression into the RZ. Results for intermittent LTRA use have been mixed, and have only been undertaken in children. Addition of ICS to as needed beta agonist use may be helpful. Strong evidence supports intermittent ICS dosing for preschool-aged children with intermittent viral-induced wheeze. However, data regarding this strategy for school-aged children and adults are limited. As for short-term increase in scheduled ICS controller, doubling the dose seems to be ineffective, while results for a more substantial increase in ICS dose (quadrupling and quintupling) have been mixed. As for dynamic dosing, this strategy appears the most promising. Symptom-driven ICS+SABA seems to be efficacious for children

and adults with mild to moderate asthma controlled on daily ICS. While, in adolescents and adults with moderate to severe asthma controlled on daily ICS+LABA, using a combination of ICS+LABA as a controller and quick reliever (SMART) has also been found to reduce exacerbations. Fortunately, the prior boxed warning of asthma-related deaths in association with LABAs has been removed from medications that contain a LABA, as review of four large clinical safety trials by the United States Food and Drug Administration demonstrated that treatment of asthma with ICS+LABA does not result in significantly more serious asthma-related side effects than treatment with ICS alone³⁸.

Multiple factors can account for the difference in outcomes seen with the various YZ intervention strategies studied, including overall study design as well as the patients enrolled in the trials. For example, the length of time of symptom decay before patients initiate YZ treatment and patients' baseline adherence to their maintenance ICS likely affect outcomes. Additionally, asthma is a heterogeneous illness with multiple potential triggers of exacerbation, which may respond quite differently to various acute therapies. Phenotyping and endotyping have further revealed the heterogeneity of not only patients' underlying asthma but also associated exacerbations^{39,40}. Certainly, more studies are needed to determine the right YZ therapies for the right patients. Like all asthma interventions, this is likely to be most effective through a personalized approach as determining the trigger and mechanism of exacerbation should lead to a more targeted therapy, and hopefully optimal response.

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Table 1 Yellow Zone Treatment Strategies

Intervention	Study	Participants	Significant Findings
Scheduled SABA	None	None	None
Intermittent LTRA	Robertson et al., 2007	2-14 years old	-Reduction in health care utilization, asthma symptoms, and school and parental work absence. -No significant reduction in beta-agonist and OCS use.
	Bacharier et al., 2008	12-59 months	-Reductions in trouble breathing and interference with activity scores. -No increase in episode-free days. -No decrease in OCS use.
	Nwokoro et al., 2014	10 months – 5 years old	-No difference in unscheduled medical visits.
	Valovirta et al., 2011	6 months – 5 years old	-Reduction in beta-agonist use. -No decrease in exacerbation rate.
Intermittent ICS Dosing	Kaiser et al. (meta analysis), 2016	Preschool-age children (≤6 years old)	-Reduction in risk of exacerbation by 35% in preschool-age children with intermittent asthma or viral-triggered wheezing.
	Chong et al. (Cochrane Review), 2015	School-age children and adults	-Reduction in risk of requiring OCS (but low quality evidence due to paucity of published data).
Increase in Maintenance ICS Dose (Doubling)	Harrison et al., 2004	≥16 years old	-No effect on OCS use, lowest PEFR recorded, rise in symptom scores, highest symptom score recorded, or time to recovery for PEFR and symptom scores.
	Fitzgerald et al., 2004	≥13 years old	-No difference in terms of treatment failures (requiring systemic steroids, unscheduled healthcare visit, and asthma returning to baseline).
	Garrett et al., 1998	6-14 years old	-No difference in PEFRs (morning or evening), diurnal peak flow variability, or symptom scores two weeks following an exacerbation.
	Rice-McDonald et al., 2005	≥18 years old	-Not superior to maintaining usual ICS dose in terms of treatment failures and PEFR.
	Kew et al. (Cochrane Review), 2016	children and adults	-Did not reduce odds of needing OCS or having an unscheduled healthcare visit compared with maintenance dose.
Substantial Increase in Maintenance ICS Dose (Quadrupling or Quintupling)	Oborne et al., 2009	≥16 years old	-Reduction in exacerbations as fewer patients required treatment with OCS.
	McKeever et al., 2018	≥16 years old	-Reduction in exacerbations (requiring systemic glucocorticoids or an unscheduled health care visit)
	Jackson et al., 2018	5-11 years old	-No significant difference in rate of exacerbations requiring systemic glucocorticoids, time to first exacerbation, rate of treatment failure, symptom scores, and albuterol use during yellow zone episodes.
Symptom-Driven Use of ICS+SABA	Papi et al., 2007	Adults (18-65 years old)	-Symptom-driven use of inhaled beclomethasone 250 µg /albuterol in a single inhaler is as effective as regular use of inhaled beclomethasone (250 µg twice daily) in terms of morning PEFR and exacerbation rate.
	Calhoun et al., 2012	Adults	-No difference in rate of treatment failure between scheduled beclomethasone 40 µg (2 puffs twice daily) and symptom driven use of beclomethasone 40 µg with albuterol.
	Martinez et al., 2011	5-18 years old	-Reduction in frequency of treatment failure with symptom-driven beclomethasone 40 µg with albuterol compared to placebo.
Single Maintenance and Reliever Therapy (SMART)	Rabe et al., 2006 →	11-79 years old	-Compared to higher dose budesonide as maintenance therapy plus terbutaline for rescue, SMART resulted in greater improvements in morning PEFR, 54% lower rate of having a severe exacerbation, 90% fewer hospitalizations/ED treatments, and 77% fewer OCS treatment days.
	Bisgaard et al., 2006	4-11 years old	-Compared to fixed-dose budesonide and fixed dose combination, SMART therapy resulted in prolonged time to first exacerbation and reduction by 70-79% in rate of exacerbation requiring medical intervention. -Mild exacerbation days and nocturnal awakenings were significantly lower with SMART.
	Papi et al., 2013	≥18 years old	-Compared to maintenance beclomethasone-formoterol with a SABA for rescue, SMART was found to increase time to first exacerbation. -Number of days with mild exacerbations was also lower with SMART.
	Sobieraj et al. (systematic review and meta-analysis), 2018	4-11 years old (limited evidence); ≥12 years old	-SMART was associated with a lower risk of asthma exacerbations compared with ICS as the controller therapy (with or without a LABA) and SABA as the reliever.
	Bateman et al., 2018	≥12 years old	-SMART was noninferior to budesonide maintenance therapy with regard to the annualized rate of severe exacerbations and time to first exacerbation. -SMART was inferior in controlling symptoms based on ACQ-5 scores.
	Obyrne et al., 2018	≥12 years old	-With regard to symptom control, SMART was superior to as-needed terbutaline, but was inferior to maintenance budesonide therapy. -Exacerbation rates were similar in both the budesonide maintenance and SMART groups, and lower compared to terbutaline.

Abbreviations:

asthma control questionnaire, ACQ
inhaled corticosteroid, ICS
leukotriene receptor antagonist, LTRA
long-acting beta-agonist, LABA
maintenance and reliever, M+R
oral corticosteroids, OCS
peak expiratory flow rate, PEFR
short-acting beta-agonist, SABA
single maintenance and reliever therapy, SMART

Key Messages

- No specific evidence suggests scheduled SABA can prevent exacerbation.
- Strong evidence supports intermittent ICS dosing for preschool-aged children with intermittent viral-induced wheeze.
- Short-term doubling of ICS controller dose seems to be ineffective, while results have been mixed for a more substantial increase in ICS dose (quadrupling and quintupling).
- Dynamic dosing appears most promising as symptom-driven ICS in tandem with rescue beta-agonist use (whether short or long acting) seem to result in a decrease in exacerbations, while minimizing ICS exposure.
- 2019 GINA guidelines now recommend as a Step 1 controller for all patients ≥ 12 years old as-needed low dose ICS-formoterol (also an option as a Step 2 controller) or low dose ICS taken whenever SABA is taken (also an option as a Step 1 controller for children 6-11 years old).
- 2019 GINA guidelines now recommend as-needed low dose ICS-formoterol as the preferred reliever therapy for all Steps of asthma care