

What Is the Role of Increasing Inhaled Corticosteroid Therapy in Worsening Asthma in Children?



Elissa M. Abrams, MD^a, Stanley J. Szeffler, MD^b, and Allan B. Becker, MD^a *Winnipeg, MB, Canada; and Aurora, Colo*

The treatment of “yellow zone,” or worsening, asthma in children remains controversial. The 2018 Global Initiative for Asthma strategy recommends increasing the dose of inhaled corticosteroid (ICS) for the short (1-2 weeks) or longer (3 months) term in children older than 5 years with worsening asthma. In contrast, the National Heart, Lung, and Blood Institute’s Expert Panel Report 3 guideline for the diagnosis and management of asthma notes that doubling the dose of ICS therapy is “not sufficient” in worsening asthma, as does the Canadian Thoracic Society guideline on asthma management in children. Both guidelines do comment that higher than double dosing may be effective. In particular, the Expert Panel Report 3 guideline specifies that more than doubling the dose of ICS therapy may be useful in the emergency department management of worsening asthma, because it may prevent oral corticosteroid requirement. The Canadian Thoracic Society suggests that adolescents (older than 12 years) quadruple ICS maintenance dosing by 4- or 5-fold for 7 to 14 days with worsening asthma if there is a history of a severe exacerbation in the past year. All these recommendations were published before a recent, large randomized double-blind controlled trial by Jackson et al that further calls into question the efficacy of increased ICS dosing in worsening asthma in children. The goal of this Rostrum was to review available data and consider the role of increasing doses of ICS and potential alternative approaches to this common practice. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:842-7)

WHAT IS THE ROLE OF INCREASING INHALED CORTICOSTEROID THERAPY IN WORSENING ASTHMA IN CHILDREN?

There is only 1 observational pediatric study that supports the practice of increasing inhaled corticosteroid (ICS) therapy in worsening asthma in children (Table 1). Volovitz et al¹ prospectively studied 193 children aged 1 to 14 years with mild intermittent or mild-to-moderate persistent asthma on maintenance inhaled budesonide (100 µg twice a day) who increased budesonide dosing with worsening asthma (200 µg 4 times a day for 1 day, then 3 times a day for 2 days, then twice a day for 1 day). This study noted a clinical improvement after a mean of 1.8 ± 0.7 days, with parents able to control 94% of 1061 worsening episodes of symptoms at home (Table 1).¹ During the 3-month preenrollment period, 67% of children required oral corticosteroids to control symptoms and 33% were hospitalized, whereas during the follow-up period only 7% required oral corticosteroids and none were hospitalized. However, there was very little comment on atopic status in these children. Observational studies can indicate correlation but not causation, the study was open-label, which may influence results, and the phenomenon of regression to the mean was not accounted for.

In contrast, several randomized trials have not supported the practice of increasing the ICS dose in worsening asthma in children. Yousef et al² randomized 197 children aged 2 to 17 years with mild-to-moderate persistent asthma and at least 1 exacerbation in the previous year who were on maintenance ICS to 2, 4, or 8 times maintenance ICS dosing for 12 days with worsening asthma (with the double ICS dose group serving as the “control”).² There was no significant difference in symptom scores ($P = .844$) or systemic corticosteroid use ($P = .451$) between the groups.² A randomized, double-blind, placebo-controlled trial (RDBPCT) by Garrett et al³ of 28 children aged 6 to 14 years with mild-to-moderate asthma on daily ICS therapy (not exceeding 800 µg/d) noted that doubling ICS therapy with worsening asthma did not significantly improve peak expiratory flow, mean diurnal peak flow variability ($P = .13$ days 1-3 postexacerbation), or symptoms scores with asthma exacerbations ($P = .80$ for night wheeze, $P = .24$ for night cough, $P = .41$ for daytime cough) compared with remaining on the same ICS dose.³ However, the Yousef et al study did not include a placebo group, and the study by Garrett et al provided only a very short duration of increased ICS therapy and studied a small number of patients. Neither study commented on the atopic status of the asthmatic population.

A Cochrane review from 2016 of increased- versus stable-dose ICS for exacerbations of asthma (including 3 pediatric studies, $n = 422$) noted no reduction in unscheduled physician visits

^aDepartment of Pediatrics, Section of Allergy and Clinical Immunology, University of Manitoba, Winnipeg, MB, Canada

^bDepartment of Pediatrics, Section of Pediatric Pulmonary and Sleep Medicine, University of Colorado School of Medicine and The Breathing Institute, Children’s Hospital Colorado, Aurora, Colo

Conflicts of interest: E. M. Abrams received an unrestricted educational grant from Novartis. S. J. Szeffler has consulted for Aerocrine/Circassia, Astra Zeneca, Boehringer Ingelheim, Daiichi Sankyo, GlaxoSmithKline, Genentech, Merck, Novartis, and Roche and has received research support from the National Institutes of Health, the National Heart, Lung and Blood Institute, and the Colorado Cancer, Cardiovascular and Pulmonary Disease Program. A. B. Becker has been on the Novartis and BI advisory boards, and the GINA science committee.

Received for publication August 14, 2018; revised October 3, 2018; accepted for publication October 6, 2018.

Available online November 13, 2018.

Corresponding author: Elissa M. Abrams, MD, Department of Pediatrics, Section of Allergy and Clinical Immunology, University FE125-685 William Ave, Winnipeg, MB, Canada R3E0Z2. E-mail: elissa.abrams@gmail.com. 2213-2198

© 2018 American Academy of Allergy, Asthma & Immunology
<https://doi.org/10.1016/j.jaip.2018.10.004>

TABLE I. Studies of Increasing ICS Dose with Worsening Asthma in Children

Study	Population	Study design	Loss of control definition	Intervention to prevent exacerbations	Definition of exacerbations	Adherence monitoring	Key outcomes	Investigators' conclusions
Volovitz et al ¹	193 children aged 1-14 y with mild intermittent or mild-to-moderate persistent asthma on budesonide 100 µg BID (although could taper to as-needed therapy on the basis of clinical symptoms)	Prospective observational study	Any asthma symptom such as cough, occurring more than once during the day or recurring after beta-2 agonist, decrease in PEF, or occurrence of viral symptoms	200 µg inhaled budesonide QID × 1 d then 200 µg TID × 2 d then 200 µg BID × 1 d with exacerbation	Need to progress to oral corticosteroid therapy and/or hospitalization for asthma	Asking parents/children at follow-up visits every 2-3 mo about medication use during worsening asthma	Clinical improvement after a mean of 1.8 ± 0.7 d; parents able to control 94% of 1061 exacerbations During a 3-mo preenrollment period, 67% of children had OCS to control symptoms and 33% were hospitalized; during the follow-up period, only 7% required OCS and none were hospitalized	"Children with asthma can control their exacerbations at home using inhaled corticosteroids... Treatment...resulted in a decrease in the use of oral steroids and in hospitalization."
Yousef et al ²	197 children aged 2-17 y with mild-to-moderate persistent asthma with at least 1 exacerbation in the past 12 mo on baseline ICS therapy	Prospective single-blind randomized trial (with the double ICS dose group serving as the "control")	Decrease in peak flow values to 50%-80% of best, increasing cough for 24-72 h, wheeze for 24-72 h responsive to beta-agonist therapy	Two, 4, or 8 times maintenance ICS dose for 12 d	Need to progress to oral corticosteroid therapy	No formal adherence monitoring Verbal conversation at initiation of worsening asthma to discuss whether to increase ICS therapy and then follow-up phone calls to determine symptom scoring	NS difference in symptom scores ($P = .844$) between groups NS difference in OCS therapy between groups ($P = .451$) Trend toward reduced mean symptom score with increasing ICS at the end of the study	"We observed no difference in the need for systemic corticosteroid use in asthmatic children treated with increasing doses of ICSs early in the course of an exacerbation."
Garrett et al ³	28 children aged 6-14 y with mild-to-moderate asthma on ICS prophylaxis (not exceeding 800 µg/d)	Randomized, double-blind, placebo-controlled crossover trial	Peak expiratory flow rate <80% baseline for 24 h, woke at night with a cough/wheeze, doubling of bronchodilator requirement	Double dose of beclomethasone × 3 d compared with placebo (remaining on baseline ICS therapy)	Peak expiratory flow rate, diurnal peak flow variability, symptom scores	Home visits during worsening asthma including verifying that the study protocol was being followed	NS difference in night wheeze ($P = .80$), night cough ($P = .24$), day wheeze ($P = .41$), day cough ($P = .42$), or mean diurnal peak flow variation ($P = .13$)	"Increasing the dose of inhaled steroids at the onset of an exacerbation of asthma is ineffective and should not be included in asthma self-management plans."
Jackson et al ⁴	254 children aged 5-11 y with mild-to-moderate persistent asthma on fluticasone propionate 88 µg twice a day; predominantly atopic population (79.2% positive aeroallergen test results)	Randomized, double-blind, parallel group trial	Use of 2 doses of rescue salbutamol in 6 h (or 3 doses in 24 h), 1 night awakening due to asthma treated with salbutamol	Quintuple dose of fluticasone propionate (440 µg BID) compared with placebo (baseline ICS therapy)	Treatment with systemic corticosteroid therapy	Nightly recordings in an electronic diary	NS difference in rate of severe exacerbations ($P = .30$), time to the first severe asthma exacerbation ($P = .20$) rate of emergency department visits ($P = .30$), rate of treatment failure ($P = .70$), symptom scores ($P = .30$), or salbutamol use during exacerbations ($P = .30$) Borderline significant decrease in linear growth (difference of $-.23$ cm in linear growth per year; $P = .06$) noted in the quintupled group compared with placebo	"In children with mild-to-moderate persistent asthma treated with daily inhaled glucocorticoids, quintupling the dose at the early signs of loss of asthma control did not reduce the rate of severe asthma exacerbations or improve other asthma outcomes and may be associated with diminished linear growth."

(continued)

TABLE 1. (Continued)

Study	Population	Study design	Loss of control definition	Intervention to prevent exacerbations	Definition of exacerbations	Adherence monitoring	Key outcomes	Investigators' conclusions
McKeever et al (Fourfold Asthma Study) ⁵	1922 adolescents (≥ 16 y) and adults with asthma on ICS therapy ($\pm$ add-on therapy) who had at least 1 exacerbation in the previous year	Pragmatic, unblinded, randomized trial	Increased reliever inhaler, difficulty sleeping, decreased peak expiratory flow to below 80% of normal level	Quadruple dose of ICS therapy compared with not quadrupling ICS therapy	Treatment with systemic corticosteroids or need for unscheduled health care visit for asthma	Self-reported adherence; once monthly text message to follow action plan	Decrease in severe exacerbations in the quadrupling group compared with the nonquadrupling group (45% vs 52%, respectively; adjusted hazard ratio for time to first exacerbation, 0.81; 95% CI, 0.71-0.92; $P = .002$) Decreased systemic corticosteroid use in the quadrupling group (33% vs 40%; incidence rate ratio, 0.82; 95% CI, 0.70-0.96)	"A personalized self-management plan that included a temporary quadrupling of the dose of inhaled glucocorticoids when asthma control started to deteriorate resulted in fewer asthma exacerbations than a plan in which the dose was not increased."

BID, Twice a day; *NS*, nonsignificant; *ICS*, oral corticosteroid; *PEF*, peak expiratory flow; *PRN*, as required; *QD*, daily; *TID*, 3 times a day.

(odds ratio [OR], 0.96; 95% CI, 0.66-1.41) or acute visits (OR, 0.98; 95% CI, 0.24-3.98) when continuing a stable dose compared with increasing the dose of ICS. The authors concluded that the evidence "does not support" increasing the dose of ICS in children with mild-to-moderate asthma to treat exacerbations.⁶

Most recently, the study by Jackson et al⁴ further questioned the role of increasing ICS therapy with worsening asthma in children. In this RDBPCT, 254 children aged 5 to 11 years with mild-to-moderate persistent asthma with at least 1 exacerbation in the past year were randomized to stable-dose (88 μ g twice a day) or quintuple-dose (440 μ g twice a day) inhaled fluticasone propionate for 7 days with worsening asthma.⁴ Over the 48-week duration of the trial, there was no difference in time to the first severe asthma exacerbation ($P = .20$), rate of emergency department visits ($P = .30$), rate of treatment failure ($P = .70$), symptom scores ($P = .30$), or albuterol use during exacerbations ($P = .30$) between the groups. In fact, there were numerically more severe exacerbations in the quintupling group (relative rate, 1.3; 95% CI, 0.8-2.1) although this was not statistically significant ($P = .30$). In addition, total glucocorticoid exposure was 16% higher in the quintupled-dose group with borderline significant decrease in linear growth (difference of -0.23 cm in linear growth per year; $P = .06$) noted. There are several strengths to this study, including its study design, large sample size, extended study duration, and predominantly atopic pediatric population, which is more suggestive of persistent asthma throughout childhood.⁷ One limitation in this study is that because the participants were already receiving maintenance ICS and well controlled, the benefits of ICS on the allergic airway inflammation component were already attenuated.

In contrast to the pediatric studies, in the adult asthmatic population, a recent study by McKeever et al⁵ has shown some benefit, in particular with quadrupling ICS dosing in worsening asthma. The Fourfold Asthma Study, published at the same time as Jackson et al's study, randomized a predominantly adult asthmatic population on ICS maintenance therapy with at least 1 exacerbation in the previous year to either stable, or quadrupling, ICS dose with worsening asthma.⁵ The patients were on varying doses of baseline ICS, with approximately 22% of both the stable and quadrupling groups on high-dose baseline ICS therapy (>1000 μ g/d beclomethasone or equivalent). Of the 1922 participants, there was a decreased number of participants with a severe asthma exacerbation in the year after randomization in the quadrupling ICS group compared with the nonquadrupling group (45% vs 52%, respectively; adjusted hazard ratio, 0.81; 95% CI, 0.71-0.92; $P = .002$; number needed to treat of 14).

There are several hypothesized reasons for the discrepancy in results between the pediatric and adult populations. As noted in an accompanying editorial to the Jackson et al and McKeever et al studies, the study designs (with McKeever et al's study being open-label) and the use of combination ICS/long-acting beta-agonists by most participants in the McKeever et al study may have impacted results.⁸ It could be hypothesized that exacerbations occur faster in children, which may provide less time for increased ICS therapy to be effective, and increased ICS therapy was not always started at the first signs of worsening in these studies (eg, in the Yousef et al study, increased ICS dosing was started within 3 days of worsening asthma). There are likely phenotypic differences in worsening asthma in children, which

may explain variability in response. Differences in stringency of monitoring adherence may alter results between study populations as well. Table I provides a summary of these studies including design, age groups, attention to adherence monitoring, and conclusions. Some degree of difference between studies may be due to different definitions of worsening asthma, or exacerbations. Although the definition of exacerbations has been proposed to be “a worsening of asthma requiring the use of systemic corticosteroids to prevent a serious outcome,”⁹ the studies above used varying definitions (Table I). Finally, emerging evidence has noted that ICS particle size affects efficacy, with extrafine ICS having significantly higher odds of asthma control and lower exacerbation rates. For example, a recent systematic review and meta-analysis of 7 studies including both the pediatric population noted that overall odds of achieving asthma control were significantly higher for extrafine ICS compared with fine-particle ICS (OR, 1.34; 95% CI, 1.22-1.46) and lower exacerbation rate ratios (0.83; 95% CI, 0.73-0.97).¹⁰ Some physicians routinely consider ultrafine ICS as first choice for the preschool child where inhaler technique is often suboptimal.

WHAT OTHER APPROACHES COULD BE CONSIDERED IN WORSENING ASTHMA IN CHILDREN?

Intermittent ICS therapy

All children in the Jackson et al study were on maintenance ICS therapy, and therefore any conclusions about efficacy of higher dose ICS therapy in worsening asthma, or lack thereof, would pertain only to this population. In fact, a recent comparative effectiveness review for the US Department of Health and Human Services notes the benefit of intermittent ICS therapy for worsening asthma in children younger than 5 years not on maintenance therapy.¹¹ This perspective is supported by several randomized studies, in particular in the atopic toddler population.¹²⁻¹⁵

The Maintenance and Intermittent Inhaled Corticosteroids in Wheezing Toddlers study by Zeiger et al¹² randomized 278 atopic toddlers (age 12-53 months with a positive API, recurrent wheeze, and at least 1 exacerbation in the past year) to daily maintenance low-dose ICS use (budesonide 0.5 mg daily) or intermittent high-dose ICS use with exacerbations and no maintenance ICS (budesonide 1 mg twice a day for 7 days), and found no significant difference in multiple measures of asthma severity including frequency of exacerbations ($P = .60$) and time to first exacerbation ($P = .87$) between the groups, while allowing for lower overall steroid exposure with the intermittent approach.¹²

The Acute Management Intervention Study by Bacharier et al¹⁴ randomized 238 toddlers aged 12 to 59 months with moderate-to-severe intermittent wheeze to intermittent budesonide inhalation (1 mg twice a day), oral montelukast (4 mg once a day), or placebo (in addition to albuterol) with respiratory tract infections for a 7-day duration. Although there was no significant difference in the primary outcome of episode-free days ($P = .66$), both budesonide and montelukast demonstrated modest reductions in troubled breathing ($P = .003$) compared with placebo and interference with activity scores ($P = .01$ and $.001$, respectively), in particular in children with a positive Asthma

Predictive Index (API). Among children with a positive API, budesonide and montelukast significantly reduced area under the curves (AUCs) for trouble breathing ($P = .001$ and $P = .007$, respectively) and interference with activity ($P = .001$ and $P < .001$, respectively), whereas only montelukast significantly reduced the AUC for wheeze ($P = .049$). In contrast, in API-negative children, neither treatment significantly reduced AUCs. However, the interaction between treatment group and API status was significant only for montelukast and only for interference with activity score AUC ($P = .03$).

Ducharme et al¹⁵ randomized 129 children aged 1 to 6 years with recurrent viral-induced wheeze to very high dose inhaled fluticasone propionate (750 μ g twice a day for a maximum of 10 days) or placebo at the onset of respiratory tract infection over a period of 6 to 12 months (median, 40 weeks) and found that intermittent high-dose inhaled fluticasone reduced the rate of systemic corticosteroid use compared with placebo (8% vs 18%, respectively; 95% CI, 0.30-0.83), although the authors caution against this approach given the statistically significant decrease in rate of linear growth in the fluticasone group.¹⁵ This growth effect may be related to the frequency of use of the high-dose ICS.

The Treating Children to Prevent Exacerbations of Asthma study by Martinez et al¹³ randomized 843 children aged 5 to 18 years with mild persistent asthma to 1 of 4 different treatments—inhaled beclomethasone 40 μ g twice a day and beclomethasone/albuterol as rescue (combined group), inhaled beclomethasone 40 μ g twice a day with placebo/albuterol as rescue (daily beclomethasone group), twice-daily placebo and beclomethasone/albuterol as rescue (rescue beclomethasone group), and placebo twice a day with placebo/albuterol as rescue (placebo group). Overall, daily ICS therapy resulted in the lowest frequency of exacerbations ($P = .03$ for daily, $P = .07$ for combined, $P = .07$ for rescue compared with placebo). However, frequency of treatment failure was lower in all groups compared with placebo ($P = .012$ for combined, $P = .009$ for daily, $P = .024$ for rescue). In addition, linear growth was less in the combined and daily groups, but not in the rescue group, compared with placebo ($P < .0001$). Because rescue beclomethasone/albuterol allowed for maintenance of normal linear growth while still providing benefit, the authors concluded that ICS with albuterol use solely as rescue medication “might be an effective...strategy.”¹³ The Treating Children to Prevent Exacerbations of Asthma study indicated that intermittent ICS could provide some benefit as an intermediate step-down procedure as daily ICS is discontinued. However, intermittent ICS administered along with albuterol did not provide benefit in those already receiving daily ICS therapy, which is similar to Jackson et al’s findings that in those already on ICS, increasing ICS does not augment the effect.

A Cochrane review of intermittent versus daily ICS use (in both children and adults) noted that although daily ICS therapy was superior for asthma control, airway inflammation, and reliever use, the 2 therapies showed similar efficacy for rescue oral steroid use and rate of severe adverse events. In addition, modest growth suppression was associated with daily, compared with intermittent, ICS use.¹⁶ However, dose and frequency of use must also be a consideration with intermittent ICS use as identified in the Ducharme et al study.

Daily ICS therapy still provides the best chance of controlling symptoms and reducing the risk of asthma exacerbations. In addition, emerging evidence suggests that toddlers with a type 2 phenotype respond better to daily ICS therapy compared with intermittent ICS or leukotriene receptor antagonist therapy. For example, the individualized therapy for persistent asthma in young children study noted in a randomized study of 300 asthmatic toddlers aged 12 to 59 months that there was a preferential response to daily ICS (over daily montelukast or intermittent ICS) in atopic toddlers (aeroallergen sensitization and/or eosinophilia).¹⁷ However, in the Individualized therapy for persistent asthma in young children study, a subgroup of children responded best to intermittent ICS therapy, although predictors of best response to this therapy could not be identified.

The above studies demonstrate the value of intermittent high-dose ICS therapy in preschool children not on maintenance daily ICS therapy. Based on these studies, intermittent ICS use is recommended as an option by the Joint Task Force on Practice Parameters in those with mild-to-moderate asthma, and could be considered as a steroid-sparing option, in particular in toddlers with episodic wheeze, provided it is initiated early in the course of infection and an individualized plan is provided to the family.^{18,19}

Intermittent montelukast

In contrast to the evidence for intermittent high-dose ICS use, the studies on intermittent montelukast use have mixed results. A randomized controlled trial by Robertson et al²⁰ suggests that intermittent montelukast with viral infection is an effective therapy. This study randomized 220 children aged 2 to 14 years to montelukast or placebo at onset of a viral infection for a minimum of 7 days and noted a significant reduction in unscheduled health care resource utilization for asthma between the montelukast and placebo groups (OR, 0.65; 95% CI, 0.47-0.89), with significant reduction in symptoms and night awakenings in the montelukast versus placebo groups (14% reduction in symptoms, 8.6% reduction in nights awakened; $P = .043$) and a significant decrease in days off school/childcare and parent time off work between the groups (37% reduction and 33% reduction, respectively; $P < .0001$).²⁰

In contrast, other studies in the toddler age group have not found this intervention to be effective. The Wheeze and Intermittent Treatment trial by Nwokoro et al²¹ randomized 1358 children aged 10 months to 5 years to intermittent montelukast or placebo at each wheeze episode over a 12-month period. There was no statistically significant difference in unscheduled medical visits for wheezing episodes between the montelukast and placebo groups (mean 2.0 vs 2.3, respectively; incidence rate ratio, 0.88; 95% CI, 0.77-1.01; $P = .06$). Valovirta et al²² randomized 589 children aged 6 months to 5 years to daily montelukast, intermittent montelukast for 12 days with worsening asthma, or placebo and noted no difference in the number of asthma episodes culminating in an asthma attack over the 1-year study period ($P = .510$ daily montelukast, $P = .884$ intermittent montelukast). However, there was a significant reduction in beta-agonist use in the daily ($P = .048$) and intermittent ($P = .028$) montelukast groups compared with placebo. The Acute Management Intervention Study noted a reduction in trouble breathing, wheeze, and interference in

activity scores with intermittent montelukast compared with placebo, with an increased benefit in toddlers with a positive API (significance for interference with activity score AUC; $P = .03$).¹⁴ However, there was no significant difference in the primary outcome (proportion of episode-free days over the year).

Combination budesonide-formoterol

In adolescents, another emerging approach supported by 2 recent RDBPCTs is the use of as-needed combination budesonide-formoterol to treat worsening asthma.^{23,24} The Symbicort Given As Needed in Mild Asthma trial randomized 3849 adolescents and adults (aged 12 years and older) with mild asthma to 1 of 3 treatments: twice-daily placebo plus terbutaline as required (terbutaline group), twice-daily placebo plus inhaled budesonide-formoterol 200/6 μg as required (budesonide-formoterol group), or twice-daily inhaled budesonide 200 μg plus terbutaline as required (budesonide maintenance group). There was no significant difference between the budesonide-formoterol group and the budesonide maintenance group in exacerbations (annualized exacerbation rate, 0.07 and 0.09, respectively; rate ratio, 0.83).²³ Budesonide-formoterol was superior to terbutaline for asthma symptom control (weeks with well-controlled asthma 34.4% vs 31.1%, respectively; OR, 1.14; 95% CI, 1.00-1.30; $P = .046$). There was a 17% lower metered daily dose of ICS in the budesonide-formoterol group compared with the budesonide group.

The SYGMA2 study randomized 4215 adolescents and adults with mild asthma to receive either twice-daily placebo plus budesonide-formoterol (200/6 μg) as required or budesonide maintenance therapy with twice-daily budesonide (200 μg) plus terbutaline (0.5 mg) as required.²⁵ There was no significant difference in the groups in the primary efficacy end point of annualized rate of severe exacerbations (annualized rate, 0.11; 95% CI, 0.10-0.13, and annualized rate, 0.12; 95% CI, 0.10-0.14, respectively), and no significant difference in several secondary efficacy end points as well (time to first severe exacerbation, number of severe exacerbations resulting in an emergency room visit or hospitalization). In addition, the median daily metered dose of ICS was 75% lower in the budesonide-formoterol group than in the budesonide maintenance group (66 μg vs 267 μg , respectively).

The use of single inhaler therapy using budesonide-formoterol as maintenance and reliever had been assessed in the preadolescent population by Bisgaard et al²⁴ in an RDBPCT of 341 children 4 to 11 years old with asthma uncontrolled on maintenance ICS. The participants were randomly assigned to budesonide-formoterol (80/4.5 μg) daily as single maintenance and reliever therapy, budesonide-formoterol (80/4.5 μg) daily as maintenance with terbutaline as required (fixed combination), or a 4-fold increased dose of budesonide alone (320 μg daily) and terbutaline as required (fixed-dose budesonide).²⁴ There was increased time to exacerbation with single maintenance and reliever therapy compared with fixed-dose budesonide ($P = .02$) and fixed combination ($P < .001$ for both). Exacerbations were significantly reduced in the single inhaler group (0.08/patient vs 0.40 and 0.28, respectively, both $P < 0.001$) with approximately 1/2 dose extra per day of combined budesonide-formoterol, which had no impact on linear growth.

Although not currently approved for this indication in the United States, regular single inhaler or intermittent combination inhaled budesonide-formoterol therapy provides other possible options to manage worsening asthma in children, while decreasing overall steroid burden.

CONCLUSIONS

At this time the optimal treatment of worsening asthma in children is unclear, especially for those who are already receiving regular maintenance ICS. The preponderance of studies does not support a role for increasing the dose of ICS in the treatment of worsening asthma in children. However, given that different studies used different doses of ICS for worsening asthma (Table 1), a dose-response study may be beneficial in the future to determine whether some doses are more effective than others. It is important to realize that frequent use of intermittent very high-dose ICS could carry a risk of systemic effects.¹⁵ Based on the evaluation of published studies, it appears that intermittent use of ICS has little to no added benefit for those children who are well controlled using daily maintenance ICS.^{4,13} However, there may be some benefit of the intermittent ICS strategy in those who are discontinuing daily ICS as a step-down procedure,¹³ or possibly for the many families who are not adherent with daily maintenance ICS.

Other approaches, such as intermittent ICS therapy with short-acting bronchodilator, intermittent montelukast, or intermittent inhaled budesonide-formoterol therapy, may hold some promise in attenuating the frequency of exacerbations, depending on age and atopic status, although not all are currently approved for that approach, either in product labeling or in available guidelines. Formal approval of some of these strategies, such as intermittent budesonide-formoterol, will require additional studies by researchers in collaboration with industry and acceptance by regulatory agencies and/or within asthma guidelines.

To date, regular use of ICS provides the best chance to control symptoms and reduce the risk for asthma exacerbations, especially for those who have allergic sensitization to aeroallergens with elevated blood eosinophils.¹⁷ However, as with all approaches to therapy, effectiveness in the real world equals efficacy (as demonstrated in well-controlled studies) combined with adherence to the management plan. Intermittent or as-required therapy, either as a function of “educated noncompliance” or as directed by health care professionals, may well be preferable for many of our patients and their families. However, it must be emphasized that if these alternative strategies are used, ongoing monitoring (including when feasible pulmonary function, exhaled nitric oxide, and asthma control questionnaires) would be beneficial to ensure that daily ICS or further step-up therapy is not required.

REFERENCES

- Volovitz B, Nussinovitch M, Finkelstein Y, Harel L, Varsano I. Effectiveness of inhaled corticosteroids in controlling acute asthma exacerbations in children at home. *Clin Pediatr (Phila)* 2001;40:79-86.
- Yousef E, Hossain J, Mannan S, Skorpinski E, McGeady S. Early intervention with high-dose inhaled corticosteroids for control of acute asthma exacerbations at home and improved outcomes: a randomized controlled trial. *Allergy Asthma Proc* 2012;33:508-13.
- Garrett J, Williams S, Wong C, Holdaway D. Treatment of acute asthmatic exacerbations with an increased dose of inhaled steroid. *Arch Dis Child* 1998;79:12-7.
- Jackson DJ, Bacharier LB, Mauger DT, Boehmer S, Beigelman A, Chmiel JF, et al. Quintupling inhaled glucocorticoids to prevent childhood asthma exacerbations. *N Engl J Med* 2018;378:891-901.
- McKeever T, Mortimer K, Wilson A, Walker S, Brightling C, Skeggs A, et al. Quadrupling inhaled glucocorticoid dose to abort asthma exacerbations. *N Engl J Med* 2018;378:902-10.
- Kew KM, Quinn M, Quon BS, Ducharme FM. Increased versus stable doses of inhaled corticosteroids for exacerbations of chronic asthma in adults and children. *Cochrane database Syst Rev* 2016;CD007524.
- Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;162:1403-6.
- Bardin PG. Escalating inhaled glucocorticoids to prevent asthma exacerbations. *N Engl J Med* 2018;378:950-2.
- Fuhlbrigge A, Peden D, Aptel AJ, Boushey HA, Camargo CAJ, Gern J, et al. Asthma outcomes: exacerbations. *J Allergy Clin Immunol* 2012;129:S34-48.
- Sonnappa S, McQueen B, Postma DS, Martin RJ, Roche N, Grigg J, et al. Extrafine versus fine inhaled corticosteroids in relation to asthma control: a systematic review and meta-analysis of observational real-life studies. *J Allergy Clin Immunol Pract* 2018;6:907-915.e7.
- Sobieraj DM, Baker WL, Weeda ER, Nguyen E, Coleman CI, White CM, et al. Intermittent Inhaled Corticosteroids and Long-Acting Muscarinic Antagonists for Asthma. *Comparative Effectiveness Review No. 194. AHRQ Publication No. 17(18)-EHC027-EF*. Rockville, MD: Agency for Healthcare Research and Quality; 2018.
- Zeiger RS, Mauger D, Bacharier LB, Guilbert TW, Martinez FD, Lemanske RFJ, et al. Daily or intermittent budesonide in preschool children with recurrent wheezing. *N Engl J Med* 2011;365:1990-2001.
- Martinez FD, Chinchilli VM, Morgan WJ, Boehmer SJ, Lemanske RFJ, Mauger DT, et al. Use of beclomethasone dipropionate as rescue treatment for children with mild persistent asthma (TREXA): a randomised, double-blind, placebo-controlled trial. *Lancet (London, England)* 2011;377:650-7.
- Bacharier LB, Phillips BR, Zeiger RS, Szefer SJ, Martinez FD, Lemanske RFJ, et al. Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing. *J Allergy Clin Immunol* 2008;122:1127-1135.e8.
- Ducharme FM, Lemire C, Noya FJD, Davis GM, Alos N, Leblond H, et al. Preemptive use of high-dose fluticasone for virus-induced wheezing in young children. *N Engl J Med* 2009;360:339-53.
- Chauhan BF, Chartrand C, Ducharme FM. Intermittent versus daily inhaled corticosteroids for persistent asthma in children and adults. *Cochrane Database Syst Rev* 2013;CD009611.
- Fitzpatrick AM, Jackson DJ, Mauger DT, Boehmer SJ, Phipatanakul W, Sheehan WJ, et al. Individualized therapy for persistent asthma in young children. *J Allergy Clin Immunol* 2016;138:1608-1618.e12.
- Dinakar C, Oppenheimer J, Portnoy J, Bacharier LB, Li J, Kerckmar CM, et al. Management of acute loss of asthma control in the yellow zone: a practice parameter. *Ann Allergy Asthma Immunol* 2014;113:143-59.
- Abrams EM, Szefer SJ, Becker AB. Does inhaled steroid therapy help emerging asthma in early childhood? *Lancet Respir Med* 2017;5:827-34.
- Robertson CF, Price D, Henry R, Mellis C, Glasgow N, Fitzgerald D, et al. Short-course montelukast for intermittent asthma in children: a randomized controlled trial. *Am J Respir Crit Care Med* 2007;175:323-9.
- Nwokoro C, Pandya H, Turner S, Eldridge S, Griffiths CJ, Vulliamy T, et al. Intermittent montelukast in children aged 10 months to 5 years with wheeze (WAIT trial): a multicentre, randomised, placebo-controlled trial. *Lancet Respir Med* 2014;2:796-803.
- Valovirta E, Boza ML, Robertson CF, Verbruggen N, Smugar SS, Nelsen LM, et al. Intermittent or daily montelukast versus placebo for episodic asthma in children. *Ann Allergy Asthma Immunol* 2011;106:518-26.
- O'Byrne PM, Fitzgerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, et al. Inhaled combined budesonide-formoterol as needed in mild asthma. *N Engl J Med* 2018;378:1865-76.
- Bisgaard H, Le Roux P, Bjammer D, Dymek A, Vermeulen JH, Hultquist C. Budesonide/formoterol maintenance plus reliever therapy: a new strategy in pediatric asthma. *Chest* 2006;130:1733-43.
- Bateman ED, Reddel HK, O'Byrne PM, Barnes PJ, Zhong N, Keen C, et al. As-needed budesonide-formoterol versus maintenance budesonide in mild asthma. *N Engl J Med* 2018;378:1877-87.