

Benefits and Risks of Long-Term Asthma Management in Children: Where Are We Heading?

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Abstract International guidelines provide recommendations for a stepwise approach to the management of asthma in children 0–4 years old, 5–11 years old, and adolescents who are treated as adults. Therapy is aimed at two domains of control: current impairment and future risk. The long-term controller medications, inhaled corticosteroids (ICSs), ICSs in combination with long-acting β_2 agonists, leukotriene receptor antagonists, and immunomodulators, exhibit different efficacies for these domains. The risk:benefit ratios of the available medications need to be carefully assessed. This review briefly presents the benefits and the potential risks of available asthma medications in children to assist the practitioner in the optimal use of asthma medications. Specifically, the systemic activity of the ICSs and how to minimize their effects on growth and adrenal activity are reviewed as well as other potential adverse effects. Dosing strategies such as intermittent therapy are also assessed.

Key Points

Adequate monitoring is warranted for the effective and safe management of asthma in infants, children, and adolescents.

Inhaled corticosteroids (ICSs) remain the preferred primary therapy for the management of asthma in children.

Alternative treatment strategies such as lower doses of ICSs, combining long-acting β_2 agonist with ICSs, and using ICSs with higher therapeutic indexes can reduce the risks.

1 Introduction

Asthma remains the most common chronic disease among children worldwide [1]. In the USA, in 2010 approximately 7 million children 0–17 years old had asthma and the prevalence has increased by 0.1% per year since 2001, although recent data suggest a plateauing from 2009 to 2013 [2]. The plateau in prevalence appears to be primarily a result of a plateau in 5- to 9-year-olds and a decline in 0- to 4-year-olds with a continuing increase 10- to 17-year-olds. Whether the prevalence decline in preschool children is due to changes in actual prevalence or reluctance of practitioners to diagnose wheezing as asthma is unclear. Regardless, preschool children have greater healthcare use and morbidity than older children and acute wheezing episodes, even if infrequent, are often treated with asthma drugs, bronchodilators, and corticosteroids. Preschool

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children have been given separate criteria for the severity and management of asthma in the international Global Initiative for Asthma (GINA) and United States Expert Panel Report 3 (EPR-3) guidelines [1, 3]. However, the decision regarding when to start a long-term controller medication remains particularly difficult in this group due to the often intermittent nature, high rate of spontaneous remission of symptoms, and concerns about potential toxicity from the drugs. These factors also come into play when treating older children and adolescents who may appear to have only intermittent symptoms. The purpose of this review is to provide a perspective on the potential risks from anti-asthma medications and help balance that against risks from asthma in children. As this is primarily an expert opinion piece, extensive use of the most recent expert reviews, systematic reviews, and meta-analyses as well as clinical trials were used as references so that the reader is given more detailed information.

2 Benefits

The benefits from most asthma medications in children have been well-established and documented by national and international guidelines and are briefly outlined here and in Table 1 [1, 3]. For children 5–11 years of age and adolescents (<18 years) with persistent asthma the inhaled corticosteroids (ICSs) improve lung function and reduce symptoms, risk of exacerbations, hospitalizations, and death [3]. In infants and children <5 years long-term ICS therapy reduces symptoms and asthma exacerbations requiring systemic corticosteroids and improves some measures of lung function [3–5]. In infants and young children with intermittent asthma or viral-induced wheezing, intermittent ICS therapy reduces the risk of severe exacerbations [5]. However, the addition of inhaled long-acting β_2 agonists (LABAs) to ICSs has not produced clear benefits over ICSs alone other than improved lung function in children 5–11 years of age. In a comparison of same-dose ICS therapy alone versus combination ICS/LABA therapy there were no differences in the risk of exacerbations requiring oral corticosteroids or hospitalization but there were fewer symptoms and as-needed rescue short-

acting β_2 agonists during the day and night for the combination, although no other significant improvements were seen [6]. Compared with doubling the dose of the ICS, the addition of a LABA produced no decrease in the risk of exacerbations requiring oral corticosteroids or hospitalizations nor any difference in measures of asthma control [6]. The vast majority of these trials were parallel-group comparisons; however, an innovative crossover trial in young children and adolescents using a hierarchical endpoint of oral corticosteroid use $\rightarrow$ asthma-control days $\rightarrow$ spirometry to define preference as the endpoint found that stepping patients up who were uncontrolled on a low-dose ICS with addition of a LABA was superior to an increased ICS dose or the addition of montelukast [7].

Leukotriene receptor antagonists (LTRAs) have been used and studied extensively in children. They reduce symptoms and the risk of exacerbations requiring oral corticosteroids somewhat but do not reduce hospitalizations in children with persistent asthma and are less effective than ICS therapy [1, 8]. The US Food and Drug Administration (FDA) approval of LTRAs for children less than 6 years old was based on an extrapolation of efficacy, safety, and pharmacokinetic data. In children 2–5 years old, montelukast decreased day- and night-time asthma symptoms and use of rescue medication compared with placebo; however, no differences from placebo were found in children 6–24 months old [9, 10]. In children with the recurrent viral-induced wheezing phenotype, montelukast reduces the severity of the wheezing exacerbations somewhat but does not affect the need for oral corticosteroids or risk of hospitalizations [1, 11]. Thus, LTRAs primarily reduce the impairment domain of control but not the risk domains from asthma.

Of the various immunomodulator therapies, only omalizumab, an anti-immunoglobulin E antibody (anti-IgE) has been approved for children 6–11 years old. The anti-interleukin-5 (anti-IL-5) antibodies are not currently approved for young children (<12 years). Omalizumab therapy has produced modest reductions in symptoms, exacerbations, and hospitalizations in allergic children in a large inner-city population not completely controlled on ICS or ICS/LABA therapy [12]. In particular, omalizumab therapy resulted in a significant decrease in the risk of fall exacerbations in these children [13].

Table 1 Relative activity of long-term control therapies on impairment and risk domains of asthma control [1, 3, 6, 8]

Asthma medications	Improve symptoms	Improve lung function	Decrease exacerbation	Decrease hospitalization	Decrease mortality
ICS	+++	+++	++++	++++	++++
ICS/LABA	++++	++++	++++	++++	++++
LTRA	++	++	+/-	0	0
Omalizumab	++	++	++	++	?

ICS inhaled corticosteroid, LABA long-acting β_2 agonist, LTRA leukotriene receptor antagonist

3 Risks

3.1 Inhaled Corticosteroids

The potential risks of ICSs have been extensively reviewed over the years [14–21]. Growth suppression, hypothalamic–pituitary–adrenal (HPA) axis suppression, hyperglycemia, bone mineral accretion (BMA), dermal thinning and skin bruising, and cataract formation are all potential risks from ICS therapy [14, 15, 18]. All of these effects are dose dependent, with the risks determined by the dose and delivery system as well as the potency and pharmacokinetic properties of each molecule (Table 2) [14, 18–21]. Each newer generation of ICSs has been developed with greater topical potencies and pharmacokinetic properties to limit systemic absorption and increase lung retention and systemic clearance, which decreases the risk of adverse effects [19–21]. However, if given in high enough doses, each of the ICSs can produce unwanted effects as they all function by stimulating the same glucocorticoid receptors. In a slightly simplistic approach, the clinician can use the data from Table 2 to estimate the relative glucocorticoid systemic load provided by different ICS preparations using the following calculation: relative potency (receptor binding affinity) $\times$ percentage absorption (gastrointestinal + lung delivery) $\times$ dose. Using two of the older preparations of beclomethasone dipropionate (BDP) and flunisolide delivered using their extra-fine-particle hydrofluoroalkane propelled metered-dose inhalers (HFA-MDIs) compared

with two newer, more potent ICSs, mometasone furoate and fluticasone propionate (FP), both by dry-powder inhalers (DPIs), and the moderately potent budesonide, also by DPI, one can appreciate the disparity between products (Table 3). The last column of Table 3 lists the amount of growth suppression reported in placebo-controlled trials of at least 1-year duration in order to provide the clinical relevance of the differences in systemic load. The model is simplistic because it does not take into consideration the lung residence time that prolongs exposure to lung glucocorticoid receptors or the systemic clearance, both of which can reduce systemic steady-state concentrations and thus improve the therapeutic index (ratio of efficacy to risk) [21, 22]. Most of the ICSs have similar systemic clearances that approximate liver blood flow with the exception of ciclesonide and its active metabolite des-ciclesonide (des-CIC), which undergo extensive extra-hepatic metabolism [21]. Higher lipophilic drugs have greater retention in the lung that is reflected in larger distribution volumes and longer serum half-lives when administered as an aerosol compared with intravenously [19, 21, 22]. This is a result of the slow distribution from the lung to the serum compartment being the rate-limiting step. The newest ICS, fluticasone furoate has the longest half-life of 24 h [22].

3.1.1 Growth Suppression

ICS-induced growth suppression in childhood has been extensively reviewed in the literature in terms of

Table 2 Comparative properties of the inhaled corticosteroids that determine efficacy and safety [19–22]

ICS/dose ^a	Binding affinity ^b	Lung delivery ^c (%)	Oral bioavailability (%)	Systemic clearance (L/h)	Half-life ^d (h) [IV/inhaled]
BDP (BMP) MDI/50 and 100 μ g	0.4	50–60	20 (40)	150 (120)	0.5/2.7 (2.7)
BUD DPI/100 and 200 μ g	9.4	15–30	11	84	2.8/2.0
Nebules®/0.25, 0.5, and 1.0 mg		5–8			
CIC (des-CIC) MDI/100 and 200 μ g	0.12 (12)	50	<1	152 (228)	0.36 (3.4)/0.5 (4.8)
FLU/80 μ g	1.8	68	20	58	1.6/1.6
FF DPI/100, 200 μ g	29	15	1	65	Unknown/24
FP DPI/50, 100, and 250 μ g		15			
FP MDI/50, 125, and 250 μ g	18	20	1	66	7.8/14
MF DPI/110 and 220 μ g	23	11	<1	53	5.0/
MDI/115 and 225 μ g					

BDP beclomethasone dipropionate, *BMP* beclomethasone monopropionate the active metabolite of BDP, *BUD* budesonide, *CIC* ciclesonide, *des-CIC* des-ciclesonide the active metabolite of CIC, *DPI* dry-powder inhaler, *FF* fluticasone furoate, *FLU* flunisolide, *FP* fluticasone propionate, *ICS* inhaled corticosteroid, *IV* intravenous, *MDI* metered-dose inhaler, *MF* mometasone furoate

^a Dose is that leaving the valve for the MDIs with the exception of FLU (ex-actuator), which comes with a built in spacer (this differs from ex-actuator dose in the US labelling), that placed in the nebulizer for Nebules®, and that activated or in blister packs for DPIs

^b Receptor binding affinities of ICSs relative to dexamethasone equal to 1

^c Assuming appropriate inhalation technique

^d Prolonged half-lives for inhaled administration compared to IV with relatively rapid clearances represent large distribution volumes due to higher distribution and retention in lung tissue

Table 3 Comparison of relative systemic glucocorticoid activity and effect on growth from recommended low-dose inhaled corticosteroids [1, 3, 16]

ICS/daily dose	Systemic availability (%) (lung + oral)) × relative receptor binding affinity (glucocorticoid activity)	RSGA ^a	Annual decrease in growth (cm; mean)
BDP MDI/100 mcg	0.70 × 13.5	756	−1.1 ^b
BUD DPI/200 mcg	0.35 × 9.4	658	−0.45 ^b
FLU MDI/160 mcg	0.80 × 1.8	230	−0.17
FP DPI/100 mcg	0.16 × 18.0	270	−0.21
MF DPI/110 mcg	0.11 × 23.0	278	−0.30

BDP beclomethasone dipropionate, *BUD* budesonide, *DPI* dry-powder inhaler, *FLU* flunisolide, *FP* fluticasone propionate, *ICS* inhaled corticosteroid, *MDI* metered-dose inhaler, *MF* mometasone furoate, *RSGA* relative systemic glucocorticoid activity

^a RSGA is the product of dose × bioavailability × potency

^b Significantly less than placebo

mechanisms, dose dependency, and final outcome on adult height attainment [15–20]. Importantly, growth suppression is the most sensitive indicator of systemic activity from both ICSs and intranasal corticosteroids (INSs) occurring without measurable perturbations of the HPA axis [16, 18, 20]. Thus, regulatory agencies require growth studies in all ICS and INS products for pediatric approval and the FDA has issued a guidance on how to complete these studies, improving our knowledge base [16]. However, as the regulatory studies are all for 1 year in prepubertal children, areas of interest for clinicians such as dose dependency, dosing frequency, age dependency, duration of therapy required to produce an effect, effect of intermittent therapy, and effect on final adult height are often missing [23]. In Childhood Asthma Management Program (CAMP), a US National Institutes of Health-funded study, 1041 children 5–12 years of age with mild-to-moderate persistent asthma were randomized to budesonide DPI (200 µg twice daily), nedocromil metered-dose inhaler (MDI) (8 mg twice daily), or matching placebos for 4–6 years (mean 4.3 years) and then followed for an additional 13 years off study drug, which helped clarify some of these issues [24]. The budesonide arm produced a significant reduction in growth velocity primarily in the first 2 years of the study that resulted in a small mean reduction in height of −1.1 cm compared with placebo [24]. As growth velocity was similar in all three groups at study end, some interpreted this as a tolerance to the effect of the ICSs or possibly an adolescent growth spurt in many of the children overcoming the effect. However, a more likely explanation was a reduction in adherence to study drug over time that is seen in many clinical trials as well as real-life situations [25]. A 3-year study reported ongoing growth suppression for the duration of the study [16]. The decreased growth velocity during the first 2 years of CAMP demonstrated a significant dose dependency of −0.1 cm/1 µg/kg ($p = 0.007$) [25]. Although the younger

children experienced greater reduction in growth velocity due to their smaller size, the lack of a significant interaction with age indicated that children entering puberty were also at risk [25]. Other studies that included both prepubertal and pubertal children also indicate no real difference in growth velocity reduction [16].

Unfortunately, many infants and young children 0–4 years of age also have persistent symptoms and risk of severe exacerbations resulting in oral corticosteroid (OCS) therapy and urgent care and hospitalizations. Although many of the ICSs are not approved in this age group, they demonstrated efficacy when administered via nebulization and with MDI plus spacers with a facemask [1–3]. Growth in this age group is primarily determined by nutrition up to 2 years and then is a combination of nutrition and growth hormone up until puberty. At first look, the growth data in this age group seems somewhat contradictory with the same doses of FP 200 µg by MDI with spacer and facemask daily showing growth suppression in some studies and not in others [5, 27, 28]. This again can be explained by a difference in dose to the patients as the AerochamberTM valved holding chamber used in a positive study delivers twice the dose of FP than the BabyhalerTM [29]. Of interest is a preliminary report indicating that the newer antistatic Aerochamber PlusTM delivers an even greater dose of FP to infants, potentially placing them at greater risk if the dose is not lowered [30]. Nebulized budesonide at 500 µg/day does not produce growth suppression but this is easily explained by the dose differential as nebulization only delivers 5% of drug and using the formula in Table 3, that dose achieves a relative systemic glucocorticoid activity of 235 vs 720 by 20% delivery of FP 200 µg by AerochamberTM MDI [31]. Thus, we need to be more cognizant of differential delivery from various devices in this population and need more studies to determine what those doses should be for control of asthma with minimal risk.

The data on dosing frequency is incomplete. We do not know whether once-daily versus twice-daily administration truly influences risk [16]. The duration of therapy required to produce growth suppression is linked with both dose dependency and the issue of intermittent therapy. Visser and colleagues performed a randomized comparative trial of FP dosing by DPI in 55 children 6–10 years old with moderate persistent asthma [32]. The children were administered either high-dose FP 1000 µg/day for 2 months followed by a reduction to 500 µg/day for 2 months, 200 µg/day for 2 months, and 100 µg/day for 1.5 years or a constant dose of 200 µg/day for 2 years. While it is notable that there were no differences in clinical efficacy between groups, the high-dose tapering group experienced a significant reduction in growth velocity, total urinary cortisol metabolites, serum osteocalcin, and amino-terminal propeptide of type 1 procollagen (both markers of bone formation) that returned to normal at 6 months, with growth velocity exceeding that of the 200 µg/day continuous dose, indicating catch-up growth. Thus, high doses of drug can produce significant effects in a short time period and may not produce a permanent decrease in height. However, a study of very high-dose intermittent FP (750 µg twice daily by MDI plus AerochamberTM for about 6 days per month) in children 1–6 years of age led to significantly less linear growth (−0.61 cm) and weight (−0.71 kg) over a 40-week period than placebo [33]. Therefore, frequent high-dose intermittent ICS therapy may also reduce growth, albeit at a lower level than that found with BDP or budesonide given continuously at low doses. Still, some investigators posit that the cumulative dose of ICSs is an important determinant of risk [31, 33]. However, the data from Visser and colleagues [32] contradicts this, with an almost three-fold increase in the cumulative dose of FP in the first 6 months of therapy compared with continuous dosing and the same growth velocity by 8 months. In the CAMP trial, when adherence began to decline significantly after the first 2 years but patients continued to take some drug, growth velocity was not further suppressed [25, 26].

Finally, the issue regarding whether growth suppression in children will affect their final adult height has been discussed over many years [1, 3, 14, 15]. In the only longitudinal prospective trial that continued to follow children into adulthood following discontinuation of study drug, the CAMP trial demonstrated that the adults, who consisted of 90% of the original cohort, still had a mean reduction of −1.2 cm in the budesonide group compared with the placebo group ($p = 0.001$) [26]. How long therapy must be continued to induce persistence is unclear. The study by Visser and colleagues [32] would suggest that 4 months of high-dose ICSs resulting in significant suppression of growth velocity did not result in a persistent decrement in

height. However, an older study of BDP administration for 7 months did not show a rebound 4 months after discontinuation [16]. Age at institution of therapy may also play a role. Guilbert and colleagues [5] used an FP 200 µg/day MDI with AerochamberTM and facemask for 2 years in infants 2–3 years old [5]. They reported a −1.7 cm difference after 2 years of therapy and only a −0.7 cm difference a year after discontinuing therapy. After another 1 year of follow-up involving 71% of the cohort, only a non-significant −0.2 cm difference was found, which was primarily driven by the youngest and smallest group (2 years old and <15 kg) at entry into the study, again suggesting a weight-dependent dose effect [28]. This suggests that most infants <4 years of age may still outgrow any growth effects once ICS therapy is either stopped or reduced. However, using lower doses of therapy that will not produce suppression but treat symptoms is likely the better alternative.

3.1.2 Bone Metabolism

Data on corticosteroid effects on bone metabolism, particularly bone mineral density (BMD), are often combined with the effects on growth, which is unfortunate because the mechanisms of alteration and dose dependency are quite different. In addition, in children, unlike adults, the issue is a decrease in BMA as opposed to increased loss of BMD. In adults, low BMD is associated with high doses of ICSs in association with other risks such as severe asthma, elderly, chronic obstructive pulmonary disease, lack of physical activity, and post-menopause [14]. In children, decreased BMA is associated with nutrition, decreased outdoor activity (sunlight), and lack of weight-bearing physical exercise; however, most cross-sectional studies have not shown an association with low- to medium-dose ICS therapy and nor have long-term prospective placebo-controlled trials [15, 16]. Although the study by Visser and colleagues [32] reported markedly depressed markers of bone formation with high-dose FP by DPI in the first 4 months, these returned to normal following reduction of the dose and did not result in different BMD Z-scores at 1 and 2 years on low doses. The CAMP trial examined BMDs over a median of 7 years and found a small decrease in annual BMA in boys but not girls that was not associated with a risk in osteopenia [24]. Unfortunately, there are no long-term studies of children on high-dose ICS therapy.

The potential detrimental effect of multiple short courses (bursts) of OCSs, primarily prednisone, on BMA and the risk of osteopenia and fractures is much more significant. An increased risk of fracture has been reported to occur in association with four or more burst of OCSs annually [16]. The CAMP trial lends support to a differential effect of OCSs on BMA, where boys receiving five

or more bursts over a median of 7 years were at risk for a significantly reduced BMA and an increased risk of osteopenia [24]. Of interest, a follow-up study demonstrated that the patients at risk for osteopenia were vitamin D (VitD) insufficient [34]. This finding may provide a way of reducing the risk of decreased BMA in children with asthma. As VitD insufficiency has been associated with an increased risk of emergency department visits and hospitalization for asthma exacerbations, it may have a two-pronged effect and also reduce the need for OCS bursts that are associated with decreased BMA.

3.1.3 Hypothalamic–Pituitary–Adrenal Axis

As with linear growth, there are numerous studies assessing the effect of ICSs on the HPA axis as these have been required by regulatory agencies, primarily standard-dose adrenal corticotrophic hormone (ACTH) stimulation and morning cortisol concentrations, for many years and more recently the FDA has approved the use of 24-h urinary free cortisol (UFC) excretion, a relatively sensitive measure of exogenous corticosteroid activity, to compare the relative systemic activity of various ICSs and dosage forms. Unfortunately, while 24-h UFC can detect small perturbations of the HPA axis, it is not particularly useful for diagnosing or predicting adrenal insufficiency [14, 15, 18]. Gold-standard tests for HPA axis insufficiency include the insulin tolerance test and metyrapone test (usually overnight), but, unlike plotting height on growth charts for children, there are no non-invasive screening measures that predict adrenal insufficiency or HPA axis insufficiency in children [35]. In a cross-sectional study of budesonide administered primarily by HFA-MDI with a spacer at a median (range) of 439 (108–1058) $\mu\text{g}/\text{m}^2$ daily, 47.5 (38.5–56.5) % of patients exhibited HPA axis suppression as measured by an overnight post-metyrapone test [36]. Only eight (6.1%) patients had abnormally low morning cortisol and only two patients with low cortisol experience signs of hypocortisolemia: nausea, vomiting, and diarrhea. Other clinical signs such as anorexia, weakness, lassitude, fatigue, dizziness, or orthostasis were uncommon in the suppressed individuals. The best predictors of suppression were the daily $\mu\text{g}/\text{m}^2$ dose of ICSs and INSs and adherence levels, but not cumulative doses of ICSs or OCSs. Finally, early morning UFC, morning cortisol, ACTH, and dehydroepiandrosterone sulfate were not predictive of suppression [37].

One has to use caution and not extrapolate the above findings from primarily budesonide use to other ICSs that may have either lower potency or bioavailability. Cases of severe adrenal insufficiency and Cushing's syndrome have occurred in children receiving FP as well as budesonide, although most of those were in association with high doses (≥ 500 $\mu\text{g}/\text{day}$) or cytochrome P450 (CYP) 3A4 inhibitors

that can markedly increase both bioavailability and decrease clearance of most of the ICSs [14, 18, 19, 38]. Case reports of adrenal crisis following long-term use of medium-dose FP have been much less frequent [18, 38]. Whether these cases might be as a result of a pharmacogenetics defect in CYP3A4 activity is unknown [39]. While much of the literature suggests that significant adrenal suppression occurs with medium to high doses of ICSs, the reports already mentioned should provide a cautionary note particularly in children receiving both ICSs and INSs concomitantly [18, 36].

Recently the Pediatric Endocrine Society Drugs and Therapeutics Committee published warnings and monitoring recommendations concerning adverse endocrine effects from ICS therapy [18]. They cautiously suggested that ciclesonide may be a preferred ICS in children experiencing HPA axis insufficiency from other ICSs, particularly FP, with a large distribution volume. However, des-CIC, the active metabolite of ciclesonide, also has a large distribution volume (Table 2), but it does have a rapid clearance that should decrease the relative systemic glucocorticoid load. While comparative studies in children between ciclesonide, FP, and budesonide report less suppression of the 24-h UFC, a recent cross-sectional study of 90 children receiving medium to high doses of either FP, budesonide, or ciclesonide used the low-dose ACTH test to determine HPA axis function and found that 7.7% were diagnosed with adrenal suppression [40]. Many patients in the ciclesonide group ($n = 3$ of 7) had suppression, as did those in the FP group ($n = 3$ of 68), suggesting that at high doses all of the ICSs pose a risk.

3.1.4 Hyperglycemia

Hyperglycemia can either be due to a decrease in insulin-stimulated glucose uptake in skeletal muscle or an increase in hepatic glucose production [14]. Hyperglycemia occurs with high-dose ICSs and is primarily a problem in patients with diabetes mellitus or who are predisposed to type 2 diabetes because of obesity [18]. Patients with pre-existing diabetes may require their anti-diabetic therapy to be adjusted.

3.1.5 Cataracts

Continuous OCS therapy is a well-known risk factor for cataract development in both children and adults [41]. In addition, high-dose ICSs is a risk factor for posterior subcapsular cataracts in high-risk elderly patients [41]. The initial CAMP trial reported one patient receiving budesonide and also courses of OCSs to have a posterior subcapsular cataract [24]. However, a follow-up study of 22% ($n = 232$) of the original cohort at 13 years found no

difference in the incidence of cataract by slit-lamp examination in patients who received corticosteroids versus those who never received corticosteroids (6.3 vs. 8.7%) [42].

3.2 Inhaled Long-Acting β_2 Agonists

The LABAs are indicated as adjunctive therapy to low- to medium-dose ICS therapy in patients whose symptoms are not completely controlled down to 4 years of age. Typical adverse effects of β_2 agonists include diastolic hypotension, which is primarily overcome by increased cardiac output, gluconeogenesis producing hyperglycemia, hypokalemia, skeletal muscle stimulation producing tremor, and widening of the corrected QT interval prolongation and ST segment depression. However, these are primarily seen with high doses when using short-acting β_2 agonists for severe acute asthma and are rarely seen with LABAs at recommended doses.

The primary issue with LABAs has been concern regarding serious asthma events (hospitalizations, intubations, and deaths) [43, 44]. An increased risk of death from asthma has been reported in adults and an increased hospitalizations reported in children with asthma in studies of the addition of LABA monotherapy to existing therapy [44]. However, a meta-analysis by the FDA of all LABA studies submitted did not show a significant increase in hospitalizations in children or any combined serious asthma events in studies including an ICS as the concomitant prescribed therapy with the LABA [43]. As this was a much smaller cohort, the FDA required all of the manufacturers that produced either LABA monotherapy or an ICS/LABA combination to perform prospective trials to determine whether LABAs in combination with an ICS posed the same risk as LABA monotherapy [44].

Three trials of 26 weeks in duration have now been completed [45–47]. Two adolescent and adult studies in over 11,600 patients each found no increased risk of serious asthma events in the LABA/ICS combination versus ICS alone group, and importantly no indication that the 11–17 years old age group had an increased risk over the older age groups as posited by the FDA [41, 46, 47]. A pediatric study in 6208 children 4–11 years old also found that the combination was not inferior to an ICS alone, with a hazard ratio with combination FP/salmeterol versus FP alone of 1.28 (95% confidence interval 0.73–2.27; $p = 0.006$) [45]. There was also no difference in height velocity over the 26 weeks between patients receiving 200 vs 500 μg daily. These trials confirm the results of the FDA meta-analysis, which found no increase in risk with combination therapy over ICS therapy alone.

3.3 Leukotriene Receptor Antagonists

Elevation of one or more hepatic enzymes has been reported with zafirlukast. Cases of life-threatening hepatic failure have also been reported with use of zafirlukast but periodic live enzyme monitoring is not recommended as early withdrawal is believed to improve the condition [1, 3]. Patients should be informed about signs and symptoms of liver dysfunction and advised to contact their physician immediately if they occur.

In 2007, based on a limited number of post-marketing suicides, US prescription information for montelukast was voluntarily updated to include “suicidal thinking and behavior” [48, 49]. In 2009, the FDA updated information on leukotriene antagonists and recommend that patients should be informed about potential neuropsychiatric events, including suicidal thinking and behavior, agitation, hallucination, aggression, anxiousness, depression, restlessness, irritability, and tremor [49]. The warning was followed by two studies assessing suicidal and behavioral-related adverse events from Merck-sponsored clinical trials of montelukast. In the clinical trials, in which more than 20,000 adults and children received montelukast, there were no reports of complete suicide; reports of possibly related to suicidal ideations were rare and similar in the control group (2.73% and 2.27%) [50, 51]. Of interest, children aged 12–17 years and adults ≥ 65 years old had a higher frequency of behavior-related adverse experiences. A large study of montelukast utilization in children using the Swedish database SWEDIS (1998–2007) reviewed 17,945 adverse events and found 45 concerning psychiatric disorders, including nightmares, unspecified anxiety, aggressiveness, sleep disorders, irritability, insomnia, hyperactivity, hallucination, and personal disorder [52]. Data are currently insufficient to suggest a direct between montelukast therapy and suicidality.

3.4 Anti-Immunoglobulin E

Omalizumab has recently been approved as adjunctive therapy for atopic for children as young as 6 years old who are incompletely responsive to ICS or ICS/LABA therapy. Few adverse effects were reported in this 60-week placebo-controlled trial in inner-city children with moderate to severe asthma [12]. Since an initial report in 2006 found that 0.09% of patients receiving omalizumab experienced anaphylaxis another 127 reports of anaphylaxis between 1 January 2006 and 31 December 2008 have been reviewed by a Joint Task Force of the American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology [53]. The new findings and recommendations were similar in that over 50% of episodes occurred with the first three doses and

within the first 2 h following administration. They therefore recommend that all patients receiving omalizumab sign an informed consent and that all new patients be observed for 2 h following the first three injections. Also, all patients should be taught how to recognize symptoms of anaphylaxis and be prescribed and taught how to use an automatic epinephrine injector. Of note, in the inner-city children study only one patient of 208 (0.005%) who received omalizumab experienced anaphylaxis compared with six of 211 (0.03%) receiving placebo [12].

4 Where to Now?

Recent studies in infants, school children, and adolescents with asthma or periodic wheezing with occasional exacerbations confirm existing guidelines recommending long-term ICS therapy as the preferred primary therapy [1, 3, 4, 19]. However, collectively we need to re-think our dosing strategies, particularly in infants receiving high-potency ICSs via MDI plus high-efficiency (non-static) spacer devices [27, 29, 30]. Although current minimal data suggest many infants may overcome the small amount of growth suppression, why risk excess systemic activity when clear alternatives of lower dosing and using ICSs with higher therapeutic indexes can reduce the risks? Unfortunately, the use of montelukast as an alternative does not reduce the risk of severe exacerbations. Other alternatives such as short courses of high doses have proven efficacy but, again, significant systemic activity occurs if the doses are too high [33]. Also, the parents of these infants need extensive education to recognize when their child is at risk of severe exacerbations [31]. We need more studies assessing dosing in these very young patients.

For children and adolescents with mild to moderate persistent asthma, low-dose ICS therapy is preferred [1, 3]. The older ICSs (BDP and budesonide) with significant oral absorption should be avoided as they produce growth suppression even at low doses [16, 17]. If monitoring of the patient's growth over the first 6 months of therapy shows decreased velocity, reconsidering the dosage used or switching ICSs is warranted. If the patients are uncontrolled on low doses and adherence and adequate device use are not the problem, it would now appear that combination therapy with a single-inhaler ICS/LABA should be the preferred option, as increasing the ICS dose, usually by doubling into the medium dose range, rarely produces improvement [19, 54]. Recent findings from the FDA-mandated LABA safety studies should alleviate the concern that LABAs might increase the risk of serious asthma exacerbations. At least in the atopic cohort, the addition of omalizumab appears to be able to reduce the risk of

exacerbations and may prevent the need for high doses of ICSs. Although a small percentage of these patients (about 15–20%) may respond to an increased dose of ICS, when moving to medium to high doses monitoring of these children for HPA axis suppression may be warranted if patients show symptoms. There simply are insufficient data on newer therapies such as long-acting anticholinergics or anti-IL-5 in children to provide a perspective.

Most large multicenter collaborative clinical trials have included collections of biomarkers, phenotypic and genetic materials to improve the predictability of response to therapies and these have been published as secondary analyses either in the primary outcomes papers or in separate publications [7, 13, 24, 31, 34]. While these secondary analyses have shown various genetic and phenotypic aspects may predict response and risks from therapy in children, they have been somewhat inconsistent and have not yet been rigorously tested in randomized clinical trials. However, a recent large trial in 12- to 59-month-old children with wheezing comparing daily ICS, montelukast, and intermittent as-needed ICS reported that daily ICS was preferable for improving symptoms and reducing exacerbations in children with aeroallergen sensitization and high eosinophils, which were pre-specified predictors [55]. There was no difference in response in those children without those predictors. Incorporating these factors into the decisions of clinicians caring for children with asthma is obviously where the future lies for improving outcomes and decreasing risks.

Finally, there is a large group of infants with viral-induced wheezing who are normal between viral infections and who are often treated with OCSs that are of questionable efficacy [56, 57]. Long-term or intermittent ICSs have not proven efficacious either [1, 19]. These patients have a reduced risk of developing severe lower respiratory tract symptoms and a reduced duration of exacerbations when treated with a course of azithromycin [58, 59]. Although there is concern regarding using antibiotics and increasing resistance in the community, this is a promising therapy; however, it requires further study.

5 Conclusion

The recommended therapies for asthma in infants, children, and adolescents are very effective and safe provided adequate monitoring of adherence, device technique, and practitioner attention to dosing is performed. In pediatrics, we are constantly reminded that one dose does not fit all. The safety profiles of the most effective therapy, ICSs, in persistent asthma is a harsh reminder of that fact.

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Conflict of interest H. William Kelly discloses the following activities: he was the Principal Investigator for the University of New Mexico site of the CAMP (Childhood Asthma Management Program) study from November 1999 to June 2011; he is currently a member of the independent Joint Oversight Committee for the four FDA-mandated LABA/ICS safety trials by AstraZeneca, GlaxoSmithKline, Merck, and Novartis and the Steering Committee for the Pediatric LABA/ICS study by GlaxoSmithKline. Hengameh Raissy discloses the following activities: she was the principal investigator for the University of New Mexico site for the CAMP Study from July 2011 to June 2012, Childhood Asthma Research Education (CARE) network 3/08-10/10 and AsthmaNet 3/11-present.

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