

Review

Endocrine Effects of Inhaled Corticosteroids in Children

Chirag R. Kapadia, MD; Todd D. Nebesio, MD; Susan E. Myers, MD; Steven Willi, MD; Bradley S. Miller, MD, PhD; David B. Allen, MD; Elka Jacobson-Dickman, MD; for the Drugs and Therapeutics Committee of the Pediatric Endocrine Society

Inhaled corticosteroids (ICSs) are widely used as first-line treatment for various chronic respiratory illnesses. Advances in devices and formulations have reduced their local adverse effects. However, as delivery of ICSs to the lungs improves, the systemic absorption increases, and an adverse effect profile similar to, although milder than, oral corticosteroids has emerged. The most serious potential adverse effect is adrenal insufficiency, which can be life threatening. Adrenal insufficiency occurs most in patients taking the highest doses of ICSs but is reported with moderate or even low doses as well. Our recommendations include greater vigilance in testing adrenal function than current standard practice. In patients with diabetes mellitus (types 1 and 2), an increase in glucose levels is likely, and diabetes medication adjustment may be needed when initiating or increasing ICSs. The risk of linear growth attenuation and adverse effects on bone mineral density is generally low but should be considered in the face of additional risk factors. On behalf of the Pediatric Endocrine Society Drugs and Therapeutics Committee, we present a review of the endocrine adverse effects of ICSs in children and offer recommendations relating to testing and referral. Limited data in particular realms diminish the strength of certain recommendations, and clinical judgment continues to be paramount.

JAMA Pediatr. 2016;170(2):163-170. doi:10.1001/jamapediatrics.2015.3526
Published online December 21, 2015.

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The members of the Drugs and Therapeutics Committee of the Pediatric Endocrine Society are listed at the end of this article.

Corresponding Author: Elka Jacobson-Dickman, MD, Division of Pediatric Endocrinology, Department of Pediatrics, Maimonides Medical Center, 4802 10th Ave, Brooklyn, NY 11219 (ejacobson-dickman@maimonidesmed.org).

Inhaled corticosteroids are widely used as effective first-line treatments for various chronic respiratory illnesses, including asthma, cystic fibrosis, and allergic rhinitis.¹ Although the long-term use of ICSs has a more favorable safety profile than oral corticosteroids, uncertainty about systemic complications persist. In children, the long-term use of oral corticosteroids can lead to compromised linear growth and bone mineralization, diabetes mellitus (types 1 and 2) (DM), Cushing syndrome, obesity, and suppression of the hypothalamic-pituitary-adrenal (HPA) axis. Inhaled corticosteroids have a similar adverse effect profile but with less frequency and severity. We review the endocrine effects of ICSs in children and the properties of the various formulations as they relate to these adverse outcomes. We have provided grading of the evidence associated with our conclusions and recommendations based on guidelines from the Centre for Evidence Based Medicine, in which a lower number indicates better evidence (scale, 1-5), and A is the highest grade of recommendation (scale, A-D).²

Case Presentation

A 7-year-old girl presented with altered mental status and a new-onset seizure. She was well until that day, when she developed cough, fatigue, and fever and then had a generalized seizure. When the ambulance arrived, her blood glucose level was 24 mg/dL (to convert to millimoles per liter, multiply by 0.0555). In the emergency department, her blood pressure was 85/50 mm

Hg, and her pulse was 125/min. The results of head imaging and a full sepsis workup were normal. Her medical history was significant for asthma and seasonal allergies. At home she took a regimen of fluticasone propionate dry powder inhaler (two 110- μ g puffs twice daily), salmeterol xinafoate (21 μ g/d), albuterol sulfate as needed, and cetirizine (10 mg/d) to which she was adherent. She had a 5-day course of prednisone 4 months prior. Her growth was normal.

She had a sodium level of 140 mEq/L (to convert to millimoles per liter, multiply by 1), and her potassium level was 4 mEq/L (to convert to millimoles per liter, multiply by 1). A serum cortisol level at the time of the hypoglycemia was low (2.1 μ g/dL) (to convert to nanomoles per liter, multiply by 27.588). Further testing revealed a morning cortisol level of 0.8 μ g/dL and an adrenocorticotropic hormone (ACTH) level less than 5 pg/mL (to convert to picomoles per liter, multiply by 0.22), suggesting central adrenal insufficiency (AI). A low-dose 1- μ g ACTH stimulation test confirmed AI with a peak cortisol level of 1.4 μ g/dL (reference range, >18 μ g/dL). Thyroid function test results, insulin-like growth factor 1 (IGF-1) levels, and prolactin levels were normal. Maintenance hydrocortisone treatment was initiated, and the family received stress dose corticosteroid education. Her pulmonologist reduced the inhaled corticosteroid (ICS) dose to 330 μ g/d after adding montelukast, and the asthma remained well controlled. The hydrocortisone dose was gradually weaned and hydrocortisone use discontinued. Six months later, an additional low-dose ACTH stimulation test result was normal with a peak stimulated cortisol level of 19.9 μ g/dL. The HPA axis suppression was attributed to her ICSs.

Dose and Formulation Effects of ICSs

Primary Conclusions

Clinical effectiveness and systemic absorption have a strong positive correlation that can only be partially addressed by device and formulation modifications (level of evidence 1).

Primary Recommendations

Device advancements have reduced local adverse effects. However, reducing the systemic adverse effects of ICSs may require increasing protein binding and rapid clearance time and decreased lipophilicity (grade of recommendation A).

Pharmacodynamics and pharmacokinetics vary among ICS formulations. This is a result of differences in oral bioavailability, glucocorticoid receptor affinity, variable deposition in the lung, volumes of distribution, lipophilic qualities, rates of clearance, and modes of delivery.^{1,3}

There are a variety of ICS delivery devices, including metered-dose inhalers, dry powder inhalers, and nebulizers; metered-dose inhalers are often used with spacer devices that reduce oral deposition and increase lung delivery. Oral deposition and lung delivery are also affected by particle size, with smaller particles having less oral and greater lung deposition.⁴ Local adverse effects, such as candidiasis, dysphonia, pharyngitis, and cough, are minimized with proper inhalation technique and postinhalation oropharyngeal rinsing. Compounds with a high rate of first-pass metabolism have less systemic drug effect from oral deposition than those with lower rates.⁵

The clinically efficacious ICS deposited in the lung is also the main source for systemic absorption^{5,6}; therefore, improved lung delivery of ICS actually increases the risk of endocrine adverse effects. Although the shift from chlorofluorocarbons to hydrofluoroalkane allows smaller particle sizes and better lung delivery for many compounds, it can also result in greater systemic absorption.⁷

There are variable degrees of cortisol suppression or systemic bioavailability among delivery devices⁸⁻¹⁰; however, for most ICSs, respiratory effectiveness correlates with systemic bioavailability. Devices that result in greater lung deposition should thus be used at lower doses. Postulation regarding the effect of discrepant intralung absorption has arisen, for example, whether there is greater systemic absorption from alveoli than bronchi, but data in this area are lacking.⁴ What appears clear, however, is that in healthy lungs or healthier asthmatic lungs, absorption is greater than in states of active disease and airflow obstruction, hence supporting clinical guidelines advocating step-down therapy for those who achieve asthma control.^{11,12}

Compounds or metabolites that are more tightly bound to albumin and other proteins and less systemically active have fewer adverse effects, as do those cleared from the circulation more rap-

At a Glance

- Inhaled corticosteroids (ICSs) are widely used as effective first-line treatment for various chronic respiratory illnesses. Although the long-term use of ICSs has a more favorable safety profile than that of oral corticosteroids, uncertainty about systemic complications persists.
- With the advancement of devices and in drug pharmacokinetics, lung delivery and bioavailability of ICSs have improved, and an adverse effect profile similar to oral corticosteroids is emerging, albeit milder and with less frequency.
- Hypothalamic-pituitary-adrenal axis suppression is a potentially life-threatening adverse effect of ICSs. Adrenal function should be tested in symptomatic patients, those with growth attenuation, and high-risk asymptomatic patients.
- Data on linear growth and bone mineral density (BMD) are generally reassuring, but height attainment should be carefully monitored, and testing for BMD should be considered in high-risk patients. Deteriorating blood glucose level control in patients with preexisting diabetes mellitus (types 1 and 2) (DM) is common with ICSs, and DM medication dose adjustments are likely required at the initiation of ICS treatment and with ICS dose increases.

idly. Although not well investigated, some experts¹³ assert that increased lipophilicity leads to greater systemic adverse effects because of wider distribution and slower clearance, particularly in the case of fluticasone. Thus, although efforts to reduce oral deposition have resulted in fewer local adverse effects, the effort to reduce systemic adverse effects may ultimately need to focus on increasing protein binding, more rapid clearance, and decreasing lipophilicity. Binding and clearance data for commonly used ICSs are summarized in Table 1.¹⁴

The compound ciclesonide hydrofluoroalkane¹⁴ is converted to a metabolite that has a high first-pass metabolism rate, is highly protein bound, is rapidly cleared, and thus would be expected to deliver clinical effect at the lungs while resulting in lower systemic consequence. However, experience with ciclesonide is not as long standing or as widespread as with fluticasone propionate dry powder inhaler, and it took many years of clinical use for endocrine adverse effects of fluticasone to surface.¹³⁻¹⁵ Thus, although the pharmacodynamic profile of ciclesonide appears to be promising, cautious optimism is recommended.

Effects on the HPA Axis

Primary Conclusions

The HPA axis suppression, although rare, is the most serious potential ICS adverse effect and can occur even in children taking standard dosages (level of evidence 1).

Table 1. Pharmacodynamics and Pharmacokinetics of Commonly Used Inhaled Glucocorticoid Formulations^a

Inhaled Glucocorticoid	Oral Bioavailability, %	Particle Size, μm	Protein Binding, %	Systemic Clearance, L/h
Beclomethasone dipropionate hydrofluoroalkane	20/40 ^b	<2.0	87	150/120 ^b
Budesonide DPI	11	>2.5	88	84
Ciclesonide hydrofluoroalkane	<1/<1 ^b	<2.0	99/99 ^b	152/228 ^b
Fluticasone propionate DPI	≤1	2.8	90	66

Abbreviation: DPI, dry powder inhaler.

^a Adapted from Ahmet et al.¹⁴

^b Active metabolite.

Table 2. Adverse Effects of ICSs

Adverse Effect	Patients at Highest Risk	Signs and Symptoms	Testing and Action	Test Result Interpretation
Growth suppression	All patients taking ICSs and additional growth-impairing medications	Decrease of >2 SDs in height or retarded growth velocity below age and pubertal norms (persisting after 1 year of therapy)	Refer to a specialist	Not applicable
Adrenal insufficiency	Symptomatic patients And asymptomatic patients with risk factors: high daily dose, taking an ICS and another corticosteroid, or low BMI	Cushingoid features, anorexia, weight loss, fatigue, growth failure, or hypoglycemia; typical symptoms of chronic adrenal insufficiency may not occur; hence, also test all high-risk asymptomatic patients	Symptomatic: if morning cortisol level ^a <3 µg/dL, adrenal insufficiency is likely; if morning cortisol level ≥3 µg/dL, 1-µg ACTH stimulation test Asymptomatic but at high risk: if morning cortisol level <3 µg/dL, 1-µg ACTH stimulation test; if morning cortisol level 3-10 µg/dL, refer to a specialist	A stimulated cortisol value <18 µg/dL is abnormal
Hyperglycemia or diabetes mellitus (types 1 and 2)	Patients with risk factors or signs of insulin resistance taking high daily dose	Polyuria, polydipsia	Annual hemoglobin A _{1c} levels and fasting glucose	Refer to a specialist if hemoglobin A _{1c} ≥6.0% or fasting glucose >100 mg/dL
Worsening blood glucose level control in diabetes mellitus (types 1 and 2)	Patients with diabetes mellitus after ICS treatment is initiated or if dose is increase	Worsening blood glucose control	Adjust diabetes medications	Not applicable
Decrease in bone mineral density	Chronic disease, malnutrition, or taking long-term medications that reduce bone mineral density	Generally asymptomatic	No routine testing unless at high risk; if not at high risk, 400- to 800-IU vitamin D supplementation and ensure adequate calcium intake	Higher-dose vitamin D supplementation for levels <30 ng/mL

Abbreviations: ACTH, adrenocorticotropic hormone; BMI, body mass index; ICS, inhaled corticosteroid.

SI conversion factors: To convert cortisol to nanomoles per liter, multiply by 27.588; glucose to millimoles per liter, multiply by 0.0555; vitamin D (25-hydroxyvitamin D) to nanomoles per liter, multiply by 2.496.

^a Morning cortisol level is defined as a serum cortisol level measured between 7 and 9 AM.

Primary Recommendations

Children taking ICSs with hypoglycemia or altered mental status should be urgently evaluated for adrenal insufficiency and treated, if necessary (grade of recommendation A). Children with growth failure, anorexia, or weight loss should be tested for AI (grade of recommendation B). Children taking high-dose ICSs or those requiring periodic oral corticosteroids treatment or additional long-term intranasal corticosteroid treatment, especially in conjunction with a low body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared), should be tested routinely (grade of recommendation C).

A testing algorithm is outlined in Table 2 and described in the text below. Stimulation testing interpretation is level of evidence 1b, as is making a diagnosis of AI from a morning cortisol level less than 3 µg/dL in a symptomatic patient.

Assurance of adrenal sufficiency in asymptomatic patients with a morning cortisol level greater than 10 µg/dL is level of evidence 5, expert opinion. Thus, if suspicion is high, one should not rely solely on adequate morning cortisol values.

It is well known that oral and injectable corticosteroids can result in suppression of the HPA axis and with prolonged use can lead to adrenocortical atrophy. After the introduction of corticosteroids in the late 1940s to treat rheumatoid arthritis, reports of sudden deaths after surgery began to emerge.¹⁶ When ICSs were introduced for asthma control, HPA axis suppression was thought to be rare but still a consideration when used at high doses for a prolonged period.^{17,18} Reassuring studies^{19,20} did not have evidence of AI at standard doses of ICSs.

In a meta-analysis²¹ examining the adverse effects of ICSs, no evidence of AI with ICS doses at 400 µg/d or less was found, regardless of the drug. At higher doses, the risk of AI was increased^{17,18,21} and common when growth suppression was also present.^{13,22}

Since then, however, there have also been reports of AI occurring even at lower doses. Patel et al²² described 8 children who presented with AI despite 7 of these children being prescribed a standard recommended dose of ICS. Two presented with hypoglycemia, both without a history of abrupt cessation of ICS or illness; several children also had poor weight gain.^{13,22} In another case, a 7-year-old boy who presented in an acute adrenal crisis had been treated with fluticasone at a typically prescribed dose of 220 µg/d for several years.¹³

As cases of AI associated with ICSs became increasingly reported, a survey was sent to pediatricians and endocrinologists in the United Kingdom to investigate the frequency of acute adrenal crises with ICS use.¹³ Thirty-three patients (28 children) were identified: 23 patients presented with hypoglycemia, including 13 with decreased level of consciousness or coma and 9 with coma and seizures (1 with coma and seizure later died). Most cases involved high-dose ICSs that were still within recommended guidelines for severe persistent asthma.¹³ In a similar survey from France, 46 patients with AI were identified, of whom 18% were not receiving high-dose ICSs.²³

It is important to acknowledge the lack of testing standardization across studies.²⁴ In cases of secondary or central AI from exogenous corticosteroid use, the adrenal cortex lags behind the pituitary gland in the recovery process.²⁵ Therefore, although a basal

cortisol level may be normal in a child treated with an ICS, it does not ensure a sufficient cortisol increase in the setting of stress or illness.²⁶ The lack of uniform testing for AI has resulted in inconsistent and conflicting conclusions.²⁶

In accordance with these concerns, Zöllner²⁷ searched the literature for studies of children treated with ICSs who were tested for AI with dynamic adrenal function test results. Only 4 studies were identified.^{19,28-30} Using dynamic adrenal testing, those studies sought to determine the prevalence of HPA axis suppression in 26 children with asthma treated with ICSs and intranasal corticosteroids.³¹ With hypocortisolemia defined as a basal morning cortisol level less than 3 µg/dL, none of the children had a low basal cortisol level. However, metyrapone testing revealed that 35% had HPA axis suppression; this test is now difficult to perform because of the unavailability of this agent. A larger study³² by the same group found that 6% had hypocortisolemia, the degree of biochemical suppression can occur in up to two-thirds of children treated with corticosteroids, and suppression may even occur at low doses. An older study²⁹ identified a morning ACTH level less than 11.7 pg/mL to correlate with AI on stimulation testing, but larger studies^{28,30,33,34} did not corroborate this finding.

Concomitant nasal corticosteroid use, low BMI, and cumulative dose of ICS are contributing factors to the development of HPA axis suppression.^{31,32} Growth failure is a late finding and is not highly sensitive for detecting HPA axis suppression.³⁰ Thus, practitioners should test most at-risk patients before growth failure occurs. However, when growth failure is detected, HPA axis function should be tested.^{22,35}

Poor adherence to ICS treatment has a protective effect, likely due to partial recovery and incomplete suppression of the adrenal glands.³² However, poor adherence also likely conversely leads to poorer asthma control and additional oral corticosteroid doses.

Our recommendations, as summarized in Table 2, include testing cortisol levels between 7 and 9 AM in all symptomatic patients not in crisis. If the morning cortisol level is less than 3 µg/dL, a diagnosis of AI is made. However, if the morning cortisol level is 3 µg/dL or greater, an ACTH stimulation test is required. Symptoms of AI in patients taking ICSs are similar to those seen with other forms of ACTH insufficiency, including anorexia, weight loss, growth failure, and hypoglycemia; unique to these cases are possible signs of apparent corticosteroid excess, such as cushingoid features.

Symptoms of adrenal crisis, such as hypotension, lethargy, and hypoglycemia, should provoke immediate testing, including a cortisol level in all cases and stimulation testing when possible. If the patient is unstable or ill appearing, treatment with stress doses of corticosteroids should be prompt while awaiting results.

We also recommend testing in certain categories of asymptomatic patients taking ICSs, including those taking high daily ICS doses or an ICS with other systemically absorbed corticosteroids, particularly patients with low BMI. The 10-µg/dL threshold is acknowledged by our group as somewhat arbitrary; however, it is widely used in clinical practice by endocrinologists. Referral for stimulation tests on all at-risk patients is impractical. With this in mind, high-risk patients should be monitored for symptoms of AI even with reassuring morning cortisol levels.

We acknowledge that although the 1-µg ACTH test is not definitely superior to the standard 250-µg ACTH stimulation test, it is generally regarded as more sensitive for secondary (central) HPA axis suppression.³⁶ At a minimum, baseline and 30-minute cortisol val-

ues should be measured, although sampling at more frequent intervals increases testing reliability (ie, 10-, 15-, 20-, and 25-minute samples).³⁷ A peak cortisol level below 18 µg/dL indicates AI.³⁸

When HPA axis suppression from ICS use is detected in symptomatic patients, daily treatment with corticosteroids are required. In milder or asymptomatic cases, treatment may be needed only in the setting of illness or physical stress. All cases of HPA axis suppression should be referred to an endocrinologist, and these patients should follow up closely with their pulmonologist or allergist for consideration of ICS dose reduction if safe, possibly by adding a corticosteroid-sparing agent (ie, leukotriene receptor antagonists).

Effects on Linear Growth

Primary Conclusions

In most patients, ICSs have minor and short-term effects on growth and very mild but potentially persistent long-term effects (level of evidence 2) (few studies followed through to final height attainment).

Primary Recommendations

The minor growth risks are outweighed by the respiratory benefits of ICSs (grade of recommendation B). Patients at higher risk include those using additional growth-impairing medications (grade of recommendation D) (primarily based on expert opinion).

Oral corticosteroids impair linear growth through suppression of growth hormone secretion, down-regulating the growth hormone receptor, reduction of IGF-1 concentration, and suppression of collagen synthesis at the growth plate.³⁹

The effect of ICSs on linear growth has been evaluated via knemometry, a technique that measures the distance from the surface of the right flexed knee to the bottom of the sole and is a precise method of monitoring short-term growth.⁴⁰⁻⁴² A placebo-controlled, crossover trial found a reduction in growth by 32% after 2 weeks of budesonide dry powder inhaler therapy.⁴¹ Similar methods have been used to reveal growth reduction with short-term therapy with other ICSs, including fluticasone and beclomethasone dipropionate hydrofluoroalkane.⁴²⁻⁴⁴ Ciclesonide, thus far, has not been found to cause major growth impairment using knemometry.⁴³

Intermediate-term investigations of the effect of ICSs on growth have found mild impairment. Using inhaled chlorofluorocarbon and beclomethasone dipropionate dry powder inhaler at 200 µg twice daily, the Dutch Pediatric Asthma Study Group⁴⁵ found a significant but small reduction in height (-0.28 SD) in 1 year. A subsequent study⁴⁶ found that doubling the dose of chlorofluorocarbon-beclomethasone dipropionate dry powder inhaler (400 µg twice daily) had a more significant effect on height (-0.27 SD) than a standard chlorofluorocarbon-beclomethasone dipropionate dry powder inhaler dose (200 µg twice daily; -0.16 SD) for 1 year, and there was no added benefit. Of note, there was a disparity in the results at the same dose from the same group, perhaps highlighting the variable short-term effects of ICSs on growth.

In a large, prospective, open-label study of both budesonide and fluticasone, Anthracopoulos et al⁴⁷ found growth reduction in both groups in the first 6 to 12 months (-0.08 SD), which was consistent with previous studies.^{48,49} However, patients' heights returned to the baseline by 24 and 36 months.

Adult height is arguably the most critical outcome measure of ICS suppressive effect on growth. Most long-term studies^{43,50,51} have found that adult heights in treated children and nontreated asthmatic control patients did not differ significantly. However, few studies^{52,53} have found a minor effect on final height of 1 cm.

Effects on Bone Mineral Density

Primary Conclusions

Inhaled corticosteroids have mild effects on bone mineral density (BMD) that usually do not reach the threshold of clinical significance (level of evidence 2). Measures to ensure vitamin D sufficiency may ameliorate the negative BMD effects of ICSs (level of evidence 4).

Primary Recommendations

Routine dual-energy X-ray absorptiometry screening in children taking ICSs without other major risk factors is not indicated (grade of recommendation B). Measures to ensure vitamin D and calcium sufficiency are indicated and in lower-risk patients taking ICSs entail routine vitamin D supplementation of 400 to 800 IU/d without monitoring vitamin D levels in blood (grade of recommendation C).

Several mechanisms impair both gastrointestinal absorption tract and renal tubular reabsorption of calcium, resulting in secondary hyperparathyroidism.⁵⁴ Furthermore, corticosteroids suppress gonadotropin-releasing hormone and inhibit both growth hormone and IGF-1 secretion and growth hormone and IGF-1 axis action, synergistically reducing BMD. Of note, corticosteroid-induced bone mineral loss occurs mainly in trabecular bone, such as the spine.³⁹

The threshold dose of ICSs for bone mineral loss has not been conclusively defined. Most pediatric studies⁵⁵⁻⁵⁸ evaluated the effects of ICSs on lumbar spine BMD by dual-energy X-ray absorptiometry. A 2003 meta-analysis⁵⁹ of 6 studies of adults included a total of 635 asthmatic patients using 4 different ICSs for at least 3 years. This analysis did not reveal a significant difference (-4.1% , $P = .80$) in lumbar BMD in patients vs controls.

Assessment of the effects of ICSs on BMD in children is confounded by variable bone accretion associated with linear growth and age at entry into puberty.⁶⁰ Several studies⁶⁰⁻⁶³ have looked at younger children to minimize the confounder of puberty. Three studies⁶⁰⁻⁶² found no deleterious effects of standard doses of beclomethasone or fluticasone on BMD in children 12 years and younger. However, a study⁶³ of 48 prepubertal children using high-dose beclomethasone or budesonide (mean [SD] dose, 670 [480] $\mu\text{g}/\text{m}^2$ daily) found a dose-dependent decrease of lumbar spine BMD accrual in 1 year in treated patients; of note, those taking oral corticosteroids were not excluded, and the study did not calculate CIs.

A study⁶⁴ evaluating BMD in 37 adolescents (mean [SD] age, 13.6 [3.3] years) treated with high-dose fluticasone propionate (mean [SD] dose, 770 [250] $\mu\text{g}/\text{m}^2$ daily) for a mean (SD) of 2.9 (1.6) years revealed that lumbar BMD was more than 1 SD below the mean in 35% of treated patients compared with controls ($P = .001$). However, when correcting for bone age, this value decreased to 16%, which was no longer statistically significant.

Overall, children receiving high-dose ICSs are at risk for substantially diminished BMD if they also have concomitant risk fac-

tors, such as frequent oral corticosteroids, malnutrition, or chronic disease. There is some evidence that optimizing vitamin D in children taking ICSs can ameliorate this effect.^{55,65} Thus, although the role of routine monitoring and titration of vitamin D supplementation is not yet established, our group considers it advisable for this group at highest risk.

For those taking ICSs without a compounding risk, routine serum vitamin D level determination is not needed. Clinicians should be cognizant of adequate vitamin D intake, prophylactically provide 400 to 800 IU/d of vitamin D, and ensure adequate dietary calcium of 1000 to 1300 mg/d.⁶⁶

Effects of Inhaled Corticosteroids on Glucose Metabolism

Primary Conclusions

The effects of ICSs on glucose levels are dose dependent. The effects of ICSs on glucose levels are primarily of concern in patients who have a previous diagnosis of DM or are at high risk of type 2 DM. These 2 conclusions are of evidence level 4 primarily because pediatric studies are limited. Data from adults in these areas are stronger.

Primary Recommendations

Patients with DM in whom ICSs are initiated or increased may require changes to their DM medication regimen. Patients at high risk of developing type 2 DM from obesity compounded by another risk factor, such as ethnicity and/or a positive family history, should be tested after ICS treatment is initiated or increased. Testing for DM is generally recommended for this population regardless of whether they are taking ICSs (grade of recommendation D). These recommendations are primarily regarded as expert opinion because pediatric studies are limited, although adult data are stronger.

The metabolic effects of corticosteroids include decreased insulin sensitivity in several tissues.⁶⁷ The decrease in insulin-stimulated glucose uptake in skeletal muscle is mediated through glucocorticoid-induced postreceptor effects.⁶⁸ Corticosteroids also cause an increase in hepatic glucose production⁶⁹ as reported by Pagano et al⁷⁰; under the influence of treatment with high-dose glucocorticoid, there was an increase in hepatic glucose production evident in both the fasted and postprandial states. However, this glucogenic effect of corticosteroids could be overcome by high concentrations of insulin, whereas skeletal muscle glucose uptake was diminished. Therefore, peripheral insulin resistance appears to be the predominant mechanism leading to corticosteroid-induced hyperglycemia. It has also been suggested that islet cell toxic effects and apoptosis occur in patients exposed to corticosteroids.⁷¹ Furthermore, corticosteroids are known to inhibit insulin secretion by pancreatic β -cells.⁷²

Inhaled corticosteroids have been implicated in contributing to clinical hyperglycemia and DM. Most studies examining this effect have been conducted in adult populations. For example, a study⁶⁹ performed in a large Veterans Affairs population suggested that, although ICSs were not associated with hyperglycemia in individuals without DM, among people with DM, ICS use was correlated with glucose levels in a dose-dependent manner. A

Table 3. Categorization of Daily Doses of Inhaled Corticosteroids^a

Corticosteroid	Daily Dose by Age, y								
	Low			Medium			High		
	0-4	5-11	>12 to Adults	0-4	5-11	>12 to Adults	0-4	5-11	>12 to Adults
Beclomethasone dipropionate hydrofluoroalkane (40 or 80 µg per puff), µg	NA	80-160	80-240	NA	>160-320	>240-480	NA	>320	>480
Budesonide									
DPI (90, 180, or 200 µg), µg	NA	180-400	180-600	NA	>400-800	<600-1200	NA	>800	>1200
Inhaled (inhaled suspension), mg	0.25-0.5	0.5	NA	>0.5-1.0	1.0	NA	>1.0	2.0	NA
Flunisolide									
Standard (250 µg per puff), µg	NA	500-750	500-1000	NA	1000-1250	>1000-2000	NA	>1250	≥2000
Hydrofluoroalkane (80 µg per puff), µg	NA	160	320	NA	320	>320-640	NA	≥640	≥640
Fluticasone dipropionate									
Hydrofluoroalkane/MDI (44, 110, or 220 µg per puff), µg	176	88-176	88-264	>176-352	>176-352	>264-440	>352mcg	>176-352	>440
DPI (50, 100, or 250 µg per puff), µg	NA	100-200	100-300	NA	>200-400	>300-500	NA	>200-400	>500
Mometasone DPI (220 µg), µg	NA	NA	200	NA	NA	400	NA	NA	<400
Triamcinolone acetonide (75 µg per puff), µg	NA	300-600	300-750	NA	>600-900	>750-1500	NA	>600-900	>1500

Abbreviations: DPI, dry powder inhaler; MDI, metered-dose inhaler; NA, not applicable because not approved, not available, no data available, or safety and efficacy not established in this age group.

^a Adapted from the National Asthma Education and Prevention Program.⁸²

number of small studies of adults^{73,74} have similarly linked hyperglycemia among diabetic individuals, but not individuals without DM, to ICS use.

Of note, a number of investigations^{75,76} have suggested that ICSs can induce insulin resistance among individuals without DM. A large epidemiologic study⁷⁷ from Canada identified a 34% to 64% higher incidence of new-onset DM among those taking ICSs, as well as a 34% to 54% higher rate of progression to insulin use among patients with established DM taking ICSs, although the researchers did not adjust for BMI. Both these studies established a dose-response association between ICS and blood glucose levels, with daily doses in excess of 1000 µg of fluticasone propionate dry powder inhaler having the most pronounced effect.

The only pediatric study⁷⁸ to date examining glycemic effects of ICSs reported a small but statistically significant increase in hemoglobin A_{1c} levels in children with asthma who were taking ICSs. However, the study failed to identify a dose-response association between ICSs and glucose levels. Furthermore, the only study⁷⁹ to examine the effects of asthma treatment on children with preexisting DM contained an insufficient number treated with ICSs to draw meaningful conclusions.

Our recommendations with regard to the effects of ICSs on glucose metabolism are summarized in Table 2. They include adjusting DM medications as needed when ICS use is initiated or ad-

justed. For children without DM, our recommendations include testing those at risk because of obesity compounded by an additional factor, such as high-risk ethnic group or family history of type 2 DM. Evidence about levels of fasting glucose and hemoglobin A_{1c} thresholds placing children into a higher DM risk category continues to be a point of debate; however, our team has chosen a fasting glucose level of 100 mg/dL and a hemoglobin A_{1c} level of 6.0% based on available data.^{80,81}

Conclusions

Inhaled corticosteroids are generally safe, effective drugs, but adverse endocrine effects may occur. Although adverse effects and the thresholds defined as high dose by asthma guidelines do not precisely correlate, for the sake of clinical practice, high dose for any particular compound is similar to that defined by the National Asthma Education and Prevention Program.⁸² We summarize dosing guidelines in Table 3. We agree with the step-up and step-down approach put forth in these guidelines,⁸² meaning that patients with poor asthma control need an increase in dosing, followed by reductions in dosing when adequate asthma control is achieved. We do not recommend decreasing the ICS dose if it is deemed necessary to prevent pulmonary exacerbations and recurrent treatment with oral corticosteroids.

ARTICLE INFORMATION

Accepted for Publication: September 20, 2015.

Published Online: December 21, 2015.

doi:10.1001/jamapediatrics.2015.3526.

Author Affiliations: Phoenix Children's Hospital, Phoenix, Arizona (Kapadia); Riley Hospital for Children, Indiana University School of Medicine, Indianapolis (Nebesio); Department of Pediatrics, St Louis University, Cardinal Glennon Children's Hospital, St Louis, Missouri (Myers); Children's

Hospital of Philadelphia, Philadelphia, Pennsylvania (Willi); University of Minnesota Masonic Children's Hospital, Minneapolis (Miller); Department of Pediatrics, University of Wisconsin School of Medicine and Public Health, Madison (Allen); Division of Pediatric Endocrinology, Department of

Pediatrics, Maimonides Medical Center, Brooklyn, New York (Jacobson-Dickman).

Author Contributions: Dr Jacobson-Dickman had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Kapadia, Nebesio, Myers, Willi, Jacobson-Dickman.

Acquisition, analysis, or interpretation of data: Kapadia, Myers, Willi, Miller, Allen.

Drafting of the manuscript: Kapadia, Nebesio, Myers, Willi, Miller, Jacobson-Dickman.

Critical revision of the manuscript for important intellectual content: Kapadia, Nebesio, Myers, Willi, Miller, Allen.

Administrative, technical, or material support: Kapadia, Myers, Willi.

Study supervision: Kapadia, Nebesio, Willi, Allen, Jacobson-Dickman.

Conflict of Interest Disclosures: None reported.

Group Information: The members of the Pediatric Endocrine Society Drug and Therapeutics Committee are Preet Brar, MD, Mark D. DeBoer, MD, Patricia Fechner, MD, Rubina Heptulla, MD, Ryan Miller, MD, Deborah Mitchell, MD, Kathleen Moltz, MD, Sriprya Raman, MD, Takara Stanley, MD, Naveen Uli, MD, and Maria Vogiatzi, MD.

Additional Contributions: We thank the Board of Directors of the Pediatric Endocrine Society for their oversight, review, and approval of the manuscript and in particular John S. Fuqua, MD, and Mitchel Geffner, MD, for their guidance.

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