Review

Endocrine Effects of Inhaled Corticosteroids in Children

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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.

Inhaled corticosteroids are widely used as effective first-line treatments for various chronic respiratory illnesses, including asthma, cystic fibrosis, and allergic rhinitis. Although the long-term use of ICSs has a more favorable safety profile than oral corticosteroids, uncertainty about systemic complications persists. 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).

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-μg puffs twice daily), salmeterol xinafoate (21 μg/d), albuterol sulfate as needed, and cetirizine (10 mg/d) to which she was adherent. Her pulmonologist reduced the inhaled corticosteroid (ICS) dose to 330 μg/d after adding montelukast, and treatment was initiated, and the family received stress dose corticosteroid education. Her pulmonologist reduced the inhaled corticosteroid (ICS) dose to 330 μg/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 μg/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 I).

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;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.11 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 rapidly. 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 1.1,14

The compound ciclesonide hydrofluoralkane14 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 I).

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.

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

<table>
<thead>
<tr>
<th>Inhaled Glucocorticoid</th>
<th>Oral Bioavailability, %</th>
<th>Particle Size, μm</th>
<th>Protein Binding, %</th>
<th>Systemic Clearance, L/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone dipropionate hydrofluorokane</td>
<td>20/40&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;2.0</td>
<td>87</td>
<td>150/120&lt;sup&gt;0&lt;/sup&gt;</td>
</tr>
<tr>
<td>Budesonide DPI</td>
<td>11</td>
<td>&gt;2.5</td>
<td>88</td>
<td>84</td>
</tr>
<tr>
<td>Ciclesonide hydrofluorokane</td>
<td>&lt;1/&lt;1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;2.0</td>
<td>99/99&lt;sup&gt;b&lt;/sup&gt;</td>
<td>152/228&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Fluticasone propionate DPI</td>
<td>≤1</td>
<td>2.8</td>
<td>90</td>
<td>66</td>
</tr>
</tbody>
</table>

Abbreviation: DPI, dry powder inhaler.

* Adapted from Ahmet et al.14
<sup>b</sup> Active metabolite.
Table 2. Adverse Effects of ICSs

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Patients at Highest Risk</th>
<th>Signs and Symptoms</th>
<th>Testing and Action</th>
<th>Test Result Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth suppression</td>
<td>All patients taking ICSs and additional growth-impairing medications</td>
<td>Decrease of &gt;2 SDs in height or retarded growth velocity below age and pubertal norms (persisting after 1 year of therapy)</td>
<td>Refer to a specialist</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>Symptomatic patients and asymptomatic patients with risk factors: high daily dose, taking an ICS and another corticosteroid, or low BMI</td>
<td>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</td>
<td>Symptomatic: if morning cortisol level* &lt;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 &lt;3 μg/dL, 1-μg ACTH stimulation test; if morning cortisol level 3-10 μg/dL, refer to a specialist</td>
<td>A stimulated cortisol value &lt;18 μg/dL is abnormal</td>
</tr>
<tr>
<td>Hyperglycemia or diabetes mellitus (types 1 and 2)</td>
<td>Patients with risk factors or signs of insulin resistance taking high daily dose</td>
<td>Polyuria, polydipsia, Annual hemoglobin A1c levels and fasting glucose</td>
<td>Refer to a specialist if hemoglobin A1c ≥6.0% or fasting glucose &gt;100 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Worsening blood glucose level control in diabetes mellitus (types 1 and 2)</td>
<td>Patients with diabetes mellitus after ICS treatment is initiated or if dose is increase</td>
<td>Worsening blood glucose control</td>
<td>Adjust diabetes medications</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Decrease in bone mineral density</td>
<td>Chronic disease, malnutrition, or taking long-term medications that reduce bone mineral density</td>
<td>Generally asymptomatic</td>
<td>No routine testing unless at high risk; if not at high risk, 400- to 800- IU vitamin D supplementation and ensure adequate calcium intake</td>
<td>Higher-dose vitamin D supplementation for levels &lt;30 ng/mL</td>
</tr>
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</table>

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 Ib, 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.14 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 studies19,20 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 increased17,18,21 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 al.23 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.13,23

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. The lack of uniform testing for AI has resulted in inconsistent and conflicting conclusions. In accordance with these concerns, Zöllner 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. 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. 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 study 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 study identified a morning ACTH level less than 11.7 pg/mL to correlate with AI on stimulation testing, but larger studies 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. Growth failure is a late finding and is not highly sensitive for detecting HPA axis suppression. Thus, practitioners should test most at-risk patients before growth failure occurs. However, when growth failure is detected, HPA axis function should be tested.

Poor adherence to ICS treatment has a protective effect, likely due to partial recovery and incomplete suppression of the adrenal glands. 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 ICSs 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 systematically 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 definitively superior to the standard 250-μg ACTH stimulation test, it is generally regarded as more sensitive for secondary (central) HPA axis suppression. At a minimum, baseline and 30-minute cortisol values should be measured, although sampling at more frequent intervals increases testing reliability (ie, 10-, 15-, 20-, and 25-minute samples). A peak cortisol level below 18 μg/dL indicates AI.

When HPA axis suppression from ICS use is detected in symptomatic patients, daily treatment with corticosteroids is 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)
Adult height is arguably the most critical outcome measure of ICS suppressive effect on growth. Most long-term studies have found that adult heights in treated children and nontreated asthmatic control patients did not differ significantly. However, few studies 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 impede both gastrointestinal absorption and renal tubular reabsorption of calcium, resulting in secondary hyperparathyroidism. 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.

The threshold dose of ICSs for bone mineral loss has not been conclusively defined. Most pediatric studies evaluated the effects of ICSs on lumbar spine BMD by dual-energy X-ray absorptiometry. A 2003 meta-analysis 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. Several studies have looked at younger children to minimize the confounder of puberty. Three studies found no deleterious effects of standard doses of beclomethasone or fluticasone on BMD in children 12 years and younger. However, a study of 48 prepubertal children using high-dose beclomethasone or budesonide (mean [SD] dose, 670 [250] μg/m² 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 study evaluating BMD in 37 adolescents (mean [SD] age, 13.6 [3.3] years) treated with high-dose fluticasone propionate (mean [SD] dose, 770 [250] μg/m² 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 factors, 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. 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.

**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. The decrease in insulin-stimulated glucose uptake in skeletal muscle is mediated through glucocorticoid-induced postreceptor effects. Corticosteroids also cause an increase in hepatic glucose production as reported by Pagano et al; 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.

Furthermore, corticosteroids are known to inhibit insulin secretion by pancreatic β-cells.

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

Of note, a number of investigations\textsuperscript{75,76} have suggested that ICSs can induce insulin resistance among individuals without DM. A large epidemiologic study\textsuperscript{77} 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 ICSs 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 study\textsuperscript{78} to date examining glycemic effects of ICSs reported a small but statistically significant increase in hemoglobin A\textsubscript{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 study\textsuperscript{79} 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 adjusted. 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\textsubscript{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\textsubscript{1c} level of 6.0\% based on available data.\textsuperscript{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.\textsuperscript{82} We summarize dosing guidelines in Table 3. We agree with the step-up and step-down approach put forth in these guidelines,\textsuperscript{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.

<table>
<thead>
<tr>
<th>Table 3. Categorization of Daily Doses of Inhaled Corticosteroids\textsuperscript{a}</th>
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<tbody>
<tr>
<td><strong>Corticosteroid</strong></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Beclomethasone dipropionate hydrofluorokane (40 or 80 μg per puff), μg</td>
</tr>
<tr>
<td>Budesonide</td>
</tr>
<tr>
<td>DPI (90, 180, or 200 μg), μg</td>
</tr>
<tr>
<td>Inhaled (inhaled suspension), mg</td>
</tr>
<tr>
<td>Fluticasone dipropionate</td>
</tr>
<tr>
<td>Hydrofluorokane/MDI (44, 110, or 220 μg per puff), μg</td>
</tr>
<tr>
<td>Hydrofluorokane (80 μg per puff), μg</td>
</tr>
<tr>
<td>Mometasone DPI (220 μg), μg</td>
</tr>
<tr>
<td>Triamcinolone acetoneide (25 μg per puff), μg</td>
</tr>
</tbody>
</table>

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.

\textsuperscript{a} Adapted from the National Asthma Education and Prevention Program.\textsuperscript{82}
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