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Adrenal Suppression from Glucocorticoids: Preventing an Iatrogenic Cause of Morbidity and Mortality in Children

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Abstract

Adrenal suppression (AS) is an important side effect of glucocorticoids (GCs) including inhaled corticosteroids (ICS). AS can often be asymptomatic or associated with non-specific symptoms until a physiological stress such as an illness precipitates an adrenal crisis. Morbidity and death associated with adrenal crisis is preventable but continues to be reported in children. There is a lack of consensus about the management of children at risk of AS. However, health care professionals need to develop an awareness and approach to keep these children safe. In this article, current knowledge of the risk factors, diagnosis and management of AS are reviewed while drawing attention to knowledge gaps and areas of controversy. Possible strategies to reduce the morbidity associated with this iatrogenic condition are provided for health care professionals.

Introduction

Glucocorticoids (GCs), including inhaled corticosteroids (ICS), are essential for the treatment of many pediatric disorders and have led to significant improvements in disease outcomes. Hypothalamic Pituitary Adrenal (HPA) axis suppression, or adrenal suppression (AS), is a potential side effect of GC therapy, and can be associated with significant morbidity and even death. [1-3]

Adrenal suppression is the most common form of adrenal insufficiency (AI) amongst both children and adults.[4,5] Despite being a treatable condition, failure of adequate preventative measures or delayed treatment has led to unnecessary morbidity and death in individuals with AI including AS.[4-6]

Symptoms of AS are often non-specific (Table 1) and can go undetected until a physiologic stress (illness, surgery, injury) precipitates an adrenal crisis. [4] Adrenal crisis has also been reported in the absence of physiologic stress, likely secondary to unrecognized signs or symptoms of AS. [2,4] Symptomatic AS including adrenal crisis can be prevented by recognizing children at risk and administering physiologic GC replacement and/or higher doses of GCs during times of stress. [3,4]

A recent study evaluating the national incidence of symptomatic AS in children in Canada reported 46 cases including 6 (13%) cases of adrenal crisis over 2 years with 37/46 (80%) of children using ICS either alone or in combination with another form of GC.[6] Asymptomatic biochemical evidence of AS is considerably more frequent with nearly 100% of patients having

AS immediately after discontinuation of high dose systemic therapy but significantly less frequent if measured after days or weeks or if exposed to other forms of GC therapy. [7-10]

Despite clear evidence of the morbidity associated with AS in the pediatric population, evidence-based guidelines about screening and management of children at risk are lacking. There are few known risk factors for the development of *symptomatic* AS, therefore the burden of screening for and managing asymptomatic biochemical AS needs to be balanced with the risk of severe morbidity and mortality in a subset of patients. There is a lack of consensus amongst pediatric endocrinologists about the approach to the management of children at risk of AS and as a result, clinicians who are prescribing GC therapy may have limited guidance about how to keep their patients safe. Within this review article, our working group comprised of pediatric endocrinologists, pediatricians and other pediatric subspecialists who frequently prescribe GC therapy present the best available evidence about AS risk, screening, testing and management while acknowledging the controversies that exist about the management of AS. The intent of this review is to draw attention to this important entity and to allow the reader to create an informed and practical approach to the management of their patients at risk.

Adrenal suppression in children treated with systemic glucocorticoids

Both clinical and biochemical evidence of AS have been well described in children following discontinuation of therapeutic doses of systemic GCs. [8,10,11] Shorter term systemic GC exposure is associated with more transient AS. [12,13] In practice, exposure for greater than 2 weeks is used as a threshold for risk of clinically important AS. [4] Duration of AS following prolonged GC exposure has been reported to be up to 2 years. [7,10] Symptomatic AS including adrenal crisis and

death are well documented related to systemic GC therapy.[3,6,11,14] Higher dose, longer duration and timing of administration of GCs (evening vs. morning) are theoretical risks. [15,16]

We did not find literature exploring risk of repeated intermittent GC exposure.

Adrenal suppression in children treated for asthma with inhaled corticosteroids

ICS therapy, when used according to current guidelines,[17,18] is rarely associated with clinically significant AS. National asthma guidelines recommend consultation with asthma specialists if children or adolescents meet criteria for treatment with high (or moderate) dose ICS therapy. [17,18]

There have been more than 90 case reports in the literature of adrenal crisis or death secondary to ICS use for the treatment of asthma. [1,19-21] Pharmacokinetic and pharmacodynamic properties and dose, in addition to ICS mode of delivery, play a role in the risk of AS[2] and therefore dose thresholds for AS risk differ between medications(see Table 2). Clinicians can consider the use of high dose ICS therapy as an important risk factor for AS, as most doses associated with increased risk correspond to high dose ICS therapy as defined by national asthma guidelines.[1,6,9,17,18,22-24] An important exception to this rule is fluticasone, an ICS that has been associated with the majority of cases of symptomatic AS in doses of 500 µg daily or greater (500 µg is moderate dosing for children ≥ 12 years in some guidelines). [1,2,6,20,25-27] . In addition, ciclesonide, a comparatively new ICS, appears to have reduced AS risk ,[2,17,18,21,25,28,29] although there is insufficient evidence about risk of AS at high doses.

In addition to high dose ICS therapy, exposure to courses of systemic GCs for treatment of asthma put children at risk of AS.[1,2,25,28] Achieving good asthma control with skilled use of controller therapy, including appropriately dosed ICS, will prevent exacerbations and reduce the need for long-term and/or repeated courses of GCs.[30] Other possible risk factors include

concomitant intranasal corticosteroids, low BMI and cumulative glucocorticoid exposure.[2,6] Duration of ICS exposure has not been found to be a risk factor, however most studies have looked at exposures of 6 weeks or more. A recent genome-wide association study suggests that a common genetic variant might lead to susceptibility to AS in patients exposed to ICS but further study is needed to support this finding.[31]

Clinicians need to be aware of the ICS doses contained in combination inhalers and should consider risk based on the ICS component (see Table 2).

Adrenal suppression in children treated with other forms of glucocorticoids

Studies of the risk of AS related to intranasal corticosteroids alone have had variable results although use in conjunction with ICS is a risk factor. [32,33,34]

While the use of low to moderate potency topical corticosteroids is rarely associated with a risk of AS[35], there have been case reports of symptomatic AS and cushingoid features in infants receiving potent topical GCs for >1 month with misuse of the medication.[36] Symptomatic AS associated with cushingoid features has also been reported with ocular GCs.[37] AS has been associated with intra-articular GCs in adults. [38]

Studies suggest that children receiving swallowed ICS for eosinophilic esophagitis or inflammatory bowel disease are at risk of AS.[6,39,40]

Medications potentiating systemic effects of glucocorticoids

CYP3A4 inhibitors, including several antiretroviral medications, antifungal agents and select antidepressants, prolong the biologic half-life of GCs. These medications have been reported (a)

in several cases of symptomatic AS associated with relatively low doses of ICS, and (b) with a prolonged duration of AS following systemic GC exposure. [8,41,42]

Glucocorticoid taper

There is no evidence to support a specific approach to GC taper for the prevention of AS. [3,43] It has been demonstrated that a gradual GC taper does not prevent AS.[10] GCs should be tapered or discontinued at a rate dictated by the underlying condition in order to maintain disease remission; if not indicated for prevention of disease relapse, a prolonged taper should be avoided to prevent unnecessary GC exposure. Physiological GC replacement should prevent symptoms of AS,[4] so testing of the HPA axis prior to discontinuing or tapering GCs below a physiological dose (<8mg/m^2/day hydrocortisone equivalent) should be considered in children who have received prolonged courses of GCs (Table 5 -GC dose equivalencies). Symptoms of GC withdrawal can occur during a rapid taper and may mimic symptoms of AS despite biochemical evidence of HPA system integrity or adequate GC replacement. [44] Clinicians need to be aware of this possibility, evaluate for possible AS, and modify their taper accordingly.

Testing for adrenal suppression

Testing for adrenal insufficiency (AI), including AS, is a challenge for clinicians due to lack of standardization of cortisol assays and lack of clinical association with established cortisol thresholds used for diagnosis.[45,46] Of particular note are newer generation assays including the Roche Cortisol II immunoassay which is reported to measure cortisol levels approximately 30% lower than the older Roche immunoassay.[47] Clinicians must be aware of the thresholds associated with the assay used in their local laboratory.

Cortisol thresholds cited within this section are reported from studies that have employed older generation immunoassays and as such, need to be interpreted with caution. First morning cortisol (7-9 am) is often used in screening for AI. A first morning cortisol is specific for diagnosis of AI if ≤100 nmol/L (≤3.6μg/dL) in individuals with a normal sleep-wake cycle in whom GCs are withheld for *at least* 24 hours.[48,49] GCs with longer duration of action must be held for longer than 24 hours. Clinicians must assess the safety of discontinuing GC therapy for testing and modify their approach accordingly (see Table 3). Since cortisol production is under circadian regulation, a low morning cortisol is poorly predictive of AS in infants and children who do not have a regular sleep-wake cycle, and dynamic testing is indicated. [50] A first morning cortisol value of ≥ 350 - 500 nmol/L (≥ 13-18μg/dL) can predict normal HPA axis function. [49,51,52] The Pediatric Endocrine Society Pharmacy and Therapeutics guideline about endocrine side effects of ICS suggests that a first morning cortisol value of 275 nmol/L (10μg/dL) may be considered as a screening threshold in asymptomatic patients [2]. However, there is no single absolute cutoff for morning cortisol that can be used to confidently rule in or out AS.

Provocative testing is typically required for diagnosis of central AI including AS. Both standard dose (250μg) and low dose (1μg) ACTH stimulation tests are used in clinical practice for evaluation of central AI with significant debate about which is superior, some studies suggesting that the low dose stimulation test (LDST) is significantly more sensitive but less specific with other studies not supporting this finding.[46,51,53] Peak cortisol thresholds of 500-600 nmol/L (18-22μg/dL) are commonly used to rule out AI but vary between studies and institutions; clinicians

must therefore refer to their local protocols for guidance. Appropriate preparation and procedures for testing of the HPA axis are required (See Table 3).

Glucocorticoid replacement

Cortisol production is significantly higher during physiological stress in healthy individuals. [54] Individuals with AI are at risk of adrenal crisis during illness, surgery or injury. Gastrointestinal illness is the most common precipitant of adrenal crisis.[55] In practice, stress dosing of GCs is provided during physiological stresses in order to prevent adrenal crisis in children with AI (Table 4). [11,14,56] There is currently insufficient data to recommend GC coverage during moderate-to-extreme activity or emotional stress. [4,57]

Hydrocortisone is the medication of choice for stress dosing, particularly during adrenal crisis because of its mineralocorticoid effect (Table 4).[55] However, in practice, while receiving active systemic GC therapy, stress dosing for moderate illness is often provided using the same form of GC that is being used to treat disease, rather than hydrocortisone (see Table 5 for relative potencies).

Children with symptomatic AS require daily physiologic GC replacement[2] (Table 4). Daily GC replacement is also an important consideration in children with clear biochemical evidence of AS[58], even in the absence of well-defined symptoms, but remains controversial among pediatric endocrinologists, with no literature supporting or refuting this approach. Hydrocortisone, with its short half-life, is the drug of choice for daily replacement with dosing of approximately 8mg/m^2/day considered to be physiological.[59,60] While three times daily (TID) hydrocortisone dosing is standard of care in primary AI,[60] many endocrinologists provide once or twice daily

dosing in AS, with higher doses in the morning to more closely mimic circadian regulation and to reduce the ongoing suppression of endogenous morning cortisol production. There is no evidence to support a specific approach. Clinicians must be aware of the short half-life of hydrocortisone and consider TID dosing if a child remains symptomatic.[4,61,62]

Strong CYP3A4 inducers, such as phenobarbital, carbamazepine or rifampicin, may decrease the serum concentration of GCs requiring an awareness of the need for dose adjustment in the context of ongoing symptoms or poor response to stress dosing in the management of AS.[63,64]

How can we reduce the risk of AS and adrenal crisis?

Despite being largely preventable, morbidity and mortality associated with AS continue to be reported. We suggest that the following measures be considered to reduce this risk:

1. Clinician education and awareness about the risk of AS including an understanding of the relatively high frequency of AS in patients being treated with *high dose* ICS therapy
2. Clinicians should prescribe the lowest effective dose of GCs with regular re-evaluation. If once-daily GC dosing is appropriate, GCs should be given in the morning to minimize suppression of the HPA axis.
3. Families should be educated about the risk of AS with an understanding that the benefits of GC therapy outweigh the risks, and that medication adherence and clinical follow-up are the best preventative measures for symptomatic AS.

4. All children with possible signs or symptoms of AS, including poor growth, and with current or recent history of GC/ICS use should be tested for AS. Symptomatic children with biochemical evidence of AS should be treated with both daily and stress dosing GC.

5. Stress dosing should be provided for critical illness or major surgery, in all children being actively treated with GCs and should be *considered* in all children who have recently discontinued GC therapy (up to a year for those with prolonged exposure) unless they have been proven to have a normal HPA axis. Cortisol should be drawn prior to initiating stress dosing during a critical illness if the diagnosis of AS is not confirmed.

6. Screening of children at high risk of AS should be considered. An alternative approach may be to provide empiric stress dosing once GC doses are tapered to <30 mg/m^2/day of hydrocortisone equivalent and for up to 6-12 months following GC discontinuation. There is no evidence to support a specific approach to asymptomatic children with AS.

7. Children with biochemical evidence of AS should receive stress dosing. Treatment with daily GC dosing should be considered.

8. Families of children with proven or suspected AS should be educated about stress dosing (Table 4) and provided with a stress dosing card or handout outlining doses, indications for stress dosing and indications to seek emergency help. Wearing a medical alert identification should be considered.

9. Family/caregiver education for administration of intramuscular (IM) hydrocortisone for use during severe illness or when unable to tolerate oral therapy, should be considered for all children with possible or proven AS, especially in those who live or travel remotely.

Conclusions

While relatively uncommon, symptomatic AS can be associated with significant morbidity and mortality. Symptomatic AS can be prevented by responsible GC prescribing and follow-up, recognition of signs and symptoms including poor growth, and screening and treatment of children at increased risk. Education of clinicians and at-risk patients/parents about AS is integral to reducing morbidity associated with this iatrogenic condition. Until further evidence is available, consultation with an endocrinologist should be considered when there is uncertainty about how to approach the management of a child or adolescent with possible or proven AS. Clinicians and families should not lose sight of the fact that GCs are essential for the management of many pediatric conditions and that the risk of AS should not be a barrier to their use.

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Table 1. Presenting symptoms and signs associated with Adrenal Suppression

Symptoms/Signs of Possible Adrenal Suppression
Poor linear growth*
Poor weight gain
Anorexia
Nausea/vomiting
Malaise
Weakness/fatigue
Headache
Abdominal pain
Myalgia/arthralgia
Psychiatric symptoms
Signs of Adrenal Crisis
Hypotension
Hypoglycemia (seizure/coma)
Signs Associated with Adrenal Suppression
Cushingoid features

*Poor linear growth has been reported in close to 50% of patients with symptomatic AS.[6] Table adapted from Ahmet et al 2011.[25]

Table 2. ICS type and dose thresholds associated with increased Adrenal Suppression risk[a]

Corticosteroid	Trade Name	Screening threshold[b] (µg/day) Canadian/European Dosing	Screening threshold[b] (µg/day) American Dosing
Beclomethasone dipropionate HFA [22]	QVAR	>400	>320
Budesonide DPI [6,22] Budesonide and formoterol	Pulmicort Turbuhaler Symbicort	≥800	≥800
Ciclesonide[c]	Alvesco	>400	>320
Fluticasone propionate [1,6,9] Fluticasone and salmeterol	Flovent MDI and spacer; Flovent Diskus; Advair	≥500	≥440 (HFA) ≥500 (DPI)
Fluticasone furoate DPI [23]	Arnuity Ellipta[d] Breo Ellipta[d]	≥100	≥100
Mometasone DPI [24] Mometasone formoterol	Asmanex Twisthaler Zenhale	≥800	≥800

[a]Threshold doses are based on the best available literature. Where no specific evidence for dose threshold for AS risk in pediatrics was available, thresholds cited are from adult studies or represent high dose therapy as per national asthma guidelines.[17,18]

[b] In the US, inhaler dose is based on the amount leaving the mouthpiece, rather than the amount leaving the canister, this accounts for differences in listed (but not actual) doses.

[c]While ciclesonide has been demonstrated to have reduced risk of systemic side effects, there is a paucity of literature about the risk of AS with high doses and as such, consideration of screening may be made at these suggested doses.

[d]Fluticasone Furoate (Arnuity Ellipta and Breo Ellipta) contain a new potent ICS. 100µg daily is equivalent to 500µg daily of fluticasone. This formulation has a high potential risk for AS. [23]

Table 3. Tests of HPA axis function: Considerations for testing

Procedure	Considerations for testing

All Tests	• Hold all oral GCs prior to the test based on their duration of action[a]:
	  ○ hydrocortisone x 24 hours,
	  ○ prednisone x 48 hours,
	  ○ dexamethasone x 72 hours
	• Consideration of a switch to hydrocortisone prior to testing should be considered in children at high risk of AS[a]
	• Hold ICS the evening and morning prior to the test if patient stable [b]

First morning cortisol [c]	• 7-9 am test (Before 8 am is optimal) • Tests drawn after 9 am must be repeated if abnormal
Low dose ACTH stimulation[h]	• Perform test in the morning[65] • 1µg corticotropin analog [f;5] • Minimal tubing length for administration of corticotropin reduces the possibility of adherence to plastic tubing[65] • Cortisol drawn at 0, 15, 30 and 60 minutes for peak levels[g;66,67]
Standard dose ACTH stimulation	• 250µg [h] corticotropin analog • Cortisol drawn at 0, 30 and 60 minutes • Currently no evidence to support morning vs afternoon testing

[a]In some cases, it may be unsafe to hold medications for the duration required. Consideration of a wean to physiological hydrocortisone dosing may be made in some circumstances to facilitate testing and address safety concerns.
[b]In children where it is unsafe to hold evening ICS dose, abnormal cortisol levels must be interpreted with caution.
[c]In infants and children with disrupted sleep-wake cycles, an abnormal first morning cortisol is not diagnostic of AS. Provocative testing is indicated.
[d]Provocative testing is required to definitively rule in or out AS
[f]Careful dilution and timely administration of corticotropin is required [65]
[g]Protocols for Low Dose ACTH stimulation tests including timing of cortisol samples may vary between institutions.
[h]For infants: corticotropin dose =15µg/kg up to a maximum dose of 250µg

Table 4. Glucocorticoid replacement and stress dosing

Indication	Glucocorticoid dose[a,b]
Adrenal crisis, severe illness or severe injury	Hydrocortisone 100 mg/m^2 (max 100 mg) IV/IM stat, then 100 mg/m^2 (max 200 mg) divided q 6 hours or by continuous infusion
Major Surgery	Hydrocortisone 50-100 mg/m^2 IV (max 100 mg) pre-op, then 100 mg/m^2/24 hrs IV (max 200 mg) by continuous infusion or divided q 6 hrs
Minor to Moderate Surgery or procedure requiring general anesthesia	Hydrocortisone 50 mg/m^2 IV (max 100 mg) pre-op, then as indicated by clinical status (typically moderate illness dosing x 1-2 days)
Moderate Illness including fever ≥38.5^o, vomiting, diarrhea, severe head cold with fatigue or injury *Able to tolerate orally*	30 mg/m^2/day hydrocortisone equivalent[c] divided TID until resolution of symptoms Duration >3 days should be reassessed by the health care team[d]
Moderate Illness including fever ≥38.5^o, vomiting, diarrhea, severe head cold with fatigue or injury *Inability to tolerate orally*	Hydrocortisone must be given parenterally 30-50 mg/m^2/day hydrocortisone divided q 6 hourly IV or q 8 hourly IM Consult endocrinology to re-assess parenteral dose if the child is still unable to tolerate orally after 24 hours of parenteral administration
Severe illness or moderate illness and unable to tolerate orally BEFORE arriving in ED	Consider teaching administration of IM hydrocortisone in all patients with AS Families who do not have rapid access to a hospital ED or who are planning remote travel (airplane, camping, etc.) should be taught administration of IM hydrocortisone
Daily Physiologic Hydrocortisone Dosing	
8 mg/m^2/day hydrocortisone daily (divided BID-TID if symptomatic with higher dose in the morning)	

[a]Poor evidence for pediatric dosing. Recommendations based on expert opinion and best available evidence. [4,60-62]

[b]Dosing may need to be adjusted in children receiving CYP3A4 Inducers. Endocrinology should be consulted in these cases.

[c]In children on active therapy in doses ≥30 mg/m^2/day hydrocortisone equivalent (≥7.5mg/m^2/day prednisone), stress dosing for mild-moderate illness can be acheived by dividing the therapeutic prednisone dose to be given BID (i.e. therapeutic dose is sufficient for stress coverage). Once therapeutic GC is no longer needed, stress dosing should be provided using hydrocortisone.

[d]Frequent or prolonged duration of stress dosing can contribute to adrenal suppression. Stress dosing is not required for very mild symptoms such as a persistent runny nose.

Table 5. Relative glucocorticoid potencies[a]

	Anti-Inflammatory Potency	HPA Suppression Potency[b]	Duration of action (hours)
Hydrocortisone (cortisol)	1	1	8 to 12
Prednisone	4	4	12 to 36
Prednisolone	4	4	12 to 36
Methylprednisolone	5	5	12 to 36
Dexamethasone	30	50 (17-100)	36 to 72

[a]HPA suppression potencies should be used when calculating hydrocortisone equivalent doses for evaluation of AS risk

[b]Available data about relative HPA suppression potency is limited and widely variable. Studies of growth suppressive effects of prednisone, prednisolone, methylprednisolone and dexamethasone suggest that secondary effects on growth relative to anti-inflammatory effects may be significantly higher. References [68-70]

References:

1. Todd GR, Acerini CL, Ross-Russell R, Zahra S, Warner JT, McCance D. Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom. Arch Dis Child 2002;87:457-61.
2. Kapadia CR, Nebesio TD, Myers SE, et al. Endocrine Effects of Inhaled Corticosteroids in Children. JAMA Pediatr 2016;170:163-70.
3. Dinsen S, Baslund B, Klose M, et al. Why glucocorticoid withdrawal may sometimes be as dangerous as the treatment itself. Eur J Intern Med 2013;24:714-20.
4. Shulman DI, Palmert MR, Kemp SF. Adrenal insufficiency: still a cause of morbidity and death in childhood. Pediatrics 2007;119:e484-94.
5. Puar TH, Stikkelbroeck NM, Smans LC, Zelissen PM, Hermus AR. Adrenal Crisis: Still a Deadly Event in the 21st Century. Am J Med 2016;129:339 e1-9.
6. Goldbloom EB, Mokashi A, Cummings EA, et al. Symptomatic adrenal suppression among children in Canada. Arch Dis Child 2017;102:338-9.
7. Wildi-Runge S, Deladoey J, Belanger C, et al. A search for variables predicting cortisol response to low-dose corticotropin stimulation following supraphysiological doses of glucocorticoids. The Journal of pediatrics 2013;163:484-8.
8. Rensen N, Gemke RJ, van Dalen EC, Rotteveel J, Kaspers GJ. Hypothalamic-pituitary-adrenal (HPA) axis suppression after treatment with glucocorticoid therapy for childhood acute lymphoblastic leukaemia. Cochrane Database Syst Rev 2017;11:CD008727.
9. Smith RW, Downey K, Gordon M, et al. Prevalence of hypothalamic-pituitary-adrenal axis suppression in children treated for asthma with inhaled corticosteroid. Paediatr Child Health 2012;17:e34-9.
10. Ahmet A, Brienza V, Tran A, et al. Frequency and Duration of Adrenal Suppression Following Glucocorticoid Therapy in Children With Rheumatic Diseases. Arthritis Care Res (Hoboken) 2017;69:1224-30.
11. Einaudi S, Bertorello N, Masera N, et al. Adrenal axis function after high-dose steroid therapy for childhood acute lymphoblastic leukemia. Pediatr Blood Cancer 2008;50:537-41.
12. Zora JA, Zimmerman D, Carey TL, O'Connell EJ, Yunginger JW. Hypothalamic-pituitary-adrenal axis suppression after short-term, high-dose glucocorticoid therapy in children with asthma. J Allergy Clin Immunol 1986;77:9-13.
13. Henzen C, Suter A, Lerch E, Urbinelli R, Schorno XH, Briner VA. Suppression and recovery of adrenal response after short-term, high-dose glucocorticoid treatment. Lancet 2000;355:542-5.
14. Rix M, Birkebaek NH, Rosthoj S, Clausen N. Clinical impact of corticosteroid-induced adrenal suppression during treatment for acute lymphoblastic leukemia in children: a prospective observational study using the low-dose adrenocorticotropin test. The Journal of pediatrics 2005;147:645-50.
15. Hawcutt DB, Jorgensen AL, Wallin N, et al. Adrenal responses to a low-dose short synacthen test in children with asthma. Clinical endocrinology 2015;82:648-56.
16. Adam HM. Fever and host responses. Pediatr Rev 1996;17:330-1.
17. Lougheed MD, Lemiere C, Ducharme FM, et al. Canadian Thoracic Society 2012 guideline update: diagnosis and management of asthma in preschoolers, children and adults. Can Respir J 2012;19:127-64.

18. www.nhlbi.nih.gov/guidelines/asthma. National Heart, Lung, and Blood Institute. National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma 2007:314. Access date: March 26, 2019.
19. Donaldson MD, Morrison C, Lees C, et al. Fatal and near-fatal encephalopathy with hyponatraemia in two siblings with fluticasone-induced adrenal suppression. Acta Paediatr 2007;96:769-72.
20. Schwartz RH, Neacsu O, Ascher DP, Alpan O. Moderate dose inhaled corticosteroid-induced symptomatic adrenal suppression: case report and review of the literature. Clinical pediatrics 2012;51:1184-90.
21. Heller MK, Laks J, Kovesi TA, Ahmet A. Reversal of adrenal suppression with ciclesonide. J Asthma 2010;47:337-9.
22. Ninan TK, Reid IW, Carter PE, Smail PJ, Russell G. Effects of high doses of inhaled corticosteroids on adrenal function in children with severe persistent asthma. Thorax 1993;48:599-602.
23. Lotvall J, Bleecker ER, Busse WW, et al. Efficacy and safety of fluticasone furoate 100 mug once-daily in patients with persistent asthma: a 24-week placebo and active-controlled randomised trial. Respir Med 2014;108:41-9.
24. Fardon TC, Lee DK, Haggart K, McFarlane LC, Lipworth BJ. Adrenal suppression with dry powder formulations of fluticasone propionate and mometasone furoate. Am J Respir Crit Care Med 2004;170:960-6.
25. Ahmet A, Kim H, Spier S. Adrenal suppression: A practical guide to the screening and management of this under-recognized complication of inhaled corticosteroid therapy. Allergy Asthma Clin Immunol 2011;7:13.
26. Zollner EW. Hypothalamic-pituitary-adrenal axis suppression in asthmatic children on inhaled corticosteroids (Part 2)--the risk as determined by gold standard adrenal function tests: a systematic review. Pediatr Allergy Immunol 2007;18:469-74.
27. Patel L, Wales JK, Kibirige MS, Massarano AA, Couriel JM, Clayton PE. Symptomatic adrenal insufficiency during inhaled corticosteroid treatment. Arch Dis Child 2001;85:330-4.
28. Lipworth BJ, Kaliner MA, LaForce CF, et al. Effect of ciclesonide and fluticasone on hypothalamic-pituitary-adrenal axis function in adults with mild-to-moderate persistent asthma. Ann Allergy Asthma Immunol 2005;94:465-72.
29. Liddell BS, Oberlin JM, Hsu DP. Inhaled corticosteroid related adrenal suppression detected by poor growth and reversed with ciclesonide. J Asthma 2017;54:99-104.
30. Guilbert TW, Morgan WJ, Zeiger RS, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. The New England journal of medicine 2006;354:1985-97.
31. Hawcutt DB, Francis B, Carr DF, et al. Susceptibility to corticosteroid-induced adrenal suppression: a genome-wide association study. Lancet Respir Med 2018;6:442-50.
32. Patel D, Ratner P, Clements D, Wu W, Faris M, Philpot E. Lack of effect on adult and adolescent hypothalamic-pituitary-adrenal axis function with use of fluticasone furoate nasal spray. Ann Allergy Asthma Immunol 2008;100:490-6.
33. Skoner DP, Berger WE, Gawchik SM, Akbary A, Qiu C. Intranasal triamcinolone and growth velocity. Pediatrics 2015;135:e348-56.

34. Zollner EW, Lombard C, Galal U, Hough S, Irusen E, Weinberg E. Hypothalamic-pituitary-adrenal axis suppression in asthmatic children on inhaled and nasal corticosteroids--more common than expected? J Pediatr Endocrinol Metab 2011;24:529-34.
35. Wood Heickman LK, Davallow Ghajar L, Conaway M, Rogol AD. Evaluation of Hypothalamic-Pituitary-Adrenal Axis Suppression following Cutaneous Use of Topical Corticosteroids in Children: A Meta-Analysis. Horm Res Paediatr 2018;89:389-96.
36. Bulus AD, Andiran N, Kocak M. Cushing's syndrome: hidden risk in usage of topical corticosteroids. J Pediatr Endocrinol Metab 2014;27:977-81.
37. Chiang MY, Sarkar M, Koppens JM, Milles J, Shah P. Exogenous Cushing's syndrome and topical ocular steroids. Eye (Lond) 2006;20:725-7.
38. Johnston PC, Lansang MC, Chatterjee S, Kennedy L. Intra-articular glucocorticoid injections and their effect on hypothalamic-pituitary-adrenal (HPA)-axis function. Endocrine 2015;48:410-6.
39. Ahmet A, Benchimol EI, Goldbloom EB, Barkey JL. Adrenal suppression in children treated with swallowed fluticasone and oral viscous budesonide for eosinophilic esophagitis. Allergy Asthma Clin Immunol 2016;12:49: eCollection 2016.
40. Cohen SA, Aloi M, Arumugam R, et al. Enteric-coated budesonide for the induction and maintenance of remission of Crohn's disease in children. Curr Med Res Opin 2017;33:1261-8.
41. Foisy MM, Yakiwchuk EM, Chiu I, Singh AE. Adrenal suppression and Cushing's syndrome secondary to an interaction between ritonavir and fluticasone: a review of the literature. HIV medicine 2008;9:389-96.
42. Bornstein SR. Predisposing factors for adrenal insufficiency. The New England journal of medicine 2009;360:2328-39.
43. Richter B, Neises G, Clar C. Glucocorticoid withdrawal schemes in chronic medical disorders. A systematic review. Endocrinology and metabolism clinics of North America 2002;31:751-78.
44. Dixon RB, Christy NP. On the various forms of corticosteroid withdrawal syndrome. Am J Med 1980;68:224-30.
45. Hawley JM, Owen LJ, Lockhart SJ, et al. Serum Cortisol: An Up-To-Date Assessment of Routine Assay Performance. Clin Chem 2016;62:1220-9.
46. Ng SM, Agwu JC, Dwan K. A systematic review and meta-analysis of Synacthen tests for assessing hypothalamic-pituitary-adrenal insufficiency in children. Arch Dis Child 2016;101:847-53.
47. Kline GA, Buse J, Krause RD. Clinical implications for biochemical diagnostic thresholds of adrenal sufficiency using a highly specific cortisol immunoassay. Clin Biochem 2017;50:475-80.
48. Maguire AM, Biesheuvel CJ, Ambler GR, Moore B, McLean M, Cowell CT. Evaluation of adrenal function using the human corticotrophin-releasing hormone test, low dose Synacthen test and 9am cortisol level in children and adolescents with central adrenal insufficiency. Clinical endocrinology 2008;68:683-91.
49. Le Roux CW, Meeran K, Alaghband-Zadeh J. Is a 0900-h serum cortisol useful prior to a short synacthen test in outpatient assessment? Ann Clin Biochem 2002;39:148-50.
50. Kazlauskaite R, Maghnie M. Pitfalls in the diagnosis of central adrenal insufficiency in children. Endocr Dev 2010;17:96-107.

51. Kazlauskaite R, Evans AT, Villabona CV, et al. Corticotropin tests for hypothalamic-pituitary- adrenal insufficiency: a metaanalysis. The Journal of clinical endocrinology and metabolism 2008;93:4245-53.
52. Woods CP, Argese N, Chapman M, et al. Adrenal suppression in patients taking inhaled glucocorticoids is highly prevalent and management can be guided by morning cortisol. European journal of endocrinology / European Federation of Endocrine Societies 2015;173:633-42.
53. Ospina NS, Al Nofal A, Bancos I, et al. ACTH Stimulation Tests for the Diagnosis of Adrenal Insufficiency: Systematic Review and Meta-Analysis. The Journal of clinical endocrinology and metabolism 2016;101:427-34.
54. Salem M, Tainsh RE, Jr., Bromberg J, Loriaux DL, Chernow B. Perioperative glucocorticoid coverage. A reassessment 42 years after emergence of a problem. Ann Surg 1994;219:416-25.
55. Oprea A, Bonnet NCG, Polle O, Lysy PA. Novel insights into glucocorticoid replacement therapy for pediatric and adult adrenal insufficiency. Ther Adv Endocrinol Metab 2019;10:2042018818821294.
56. Hahner S, Spinnler C, Fassnacht M, et al. High incidence of adrenal crisis in educated patients with chronic adrenal insufficiency: a prospective study. The Journal of clinical endocrinology and metabolism 2015;100:407-16.
57. Weise M, Drinkard B, Mehlinger SL, et al. Stress dose of hydrocortisone is not beneficial in patients with classic congenital adrenal hyperplasia undergoing short-term, high-intensity exercise. The Journal of clinical endocrinology and metabolism 2004;89:3679-84.
58. Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology 2013;9:30.
59. Linder BL, Esteban NV, Yergey AL, Winterer JC, Loriaux DL, Cassorla F. Cortisol production rate in childhood and adolescence. The Journal of pediatrics 1990;117:892-6.
60. Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. The Journal of clinical endocrinology and metabolism 2016;101:364-89.
61. Bancos I, Hahner S, Tomlinson J, Arlt W. Diagnosis and management of adrenal insufficiency. The lancet Diabetes & endocrinology 2015;3:216-26.
62. Charmandari E, Nicolaides NC, Chrousos GP. Adrenal insufficiency. Lancet 2014;383:2152-67.
63. Borcherding SM, Baciewicz AM, Self TH. Update on rifampin drug interactions. II. Arch Intern Med 1992;152:711-6.
64. Lexicomp. Lexicomp Online. Wolters Kluwer; 2016.
65. Wade M, Baid S, Calis K, Raff H, Sinaii N, Nieman L. Technical details influence the diagnostic accuracy of the 1 microg ACTH stimulation test. European journal of endocrinology / European Federation of Endocrine Societies 2010;162:109-13.
66. Cartaya J, Misra M. The low-dose ACTH stimulation test: is 30 minutes long enough? Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 2015;21:508-13.

67. Gill H WR, Barrowman N, Ahmet A. Evaluating the low-dose ACTH stimulation test: Ideal timings for cortisol measurement. Journal of Clinical Endocrinology and Metabolism 2019;In Press June 2019.
68. Treatment of adrenal insufficiency in children. UpToDate. Wolters Kluwer, 2016. (Accessed 13 October, 2016, at https://www.uptodate.com/index.html#!/contents/treatment-of-adrenal-insufficiency-in-children?source=search_result&search=glucocorticoid%20potency&selectedTitle=6~7.)
69. Punthakee Z, Legault L, Polychronakos C. Prednisolone in the treatment of adrenal insufficiency: a re-evaluation of relative potency. The Journal of pediatrics 2003;143:402-5.
70. Chrousos, Pavlaki AN, Magiakou MA. Glucocorticoid Therapy and Adrenal Suppression [Updated 2011 Jan 11]. In: De Groot LJ, Chrousos G, Dungan K, et al., eds. South Dartmouth (MA); Available from: https://www.ncbi.nlm.nih.gov/books/NBK279156/: Endotext [Internet]; 2011.

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Adrenal Suppression from Glucocorticoids: Preventing an Iatrogenic Cause of Morbidity and Mortality in Children

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Abstract

Adrenal suppression (AS) is an important side effect of glucocorticoids (GCs) including inhaled corticosteroids (ICS). AS can often be asymptomatic or associated with non-specific symptoms until a physiological stress such as an illness precipitates an adrenal crisis. Morbidity and death associated with adrenal crisis is preventable but continues to be reported in children. There is a lack of consensus about the management of children at risk of AS. However, health care professionals need to develop an awareness and approach to keep these children safe. In this article, current knowledge of the risk factors, diagnosis and management of AS are reviewed while drawing attention to knowledge gaps and areas of controversy. Possible strategies to reduce the morbidity associated with this iatrogenic condition are provided for health care professionals.

Introduction

Glucocorticoids (GCs), including inhaled corticosteroids (ICS), are essential for the treatment of many pediatric disorders and have led to significant improvements in disease outcomes. Hypothalamic Pituitary Adrenal (HPA) axis suppression, or adrenal suppression (AS), is a potential side effect of GC therapy, and can be associated with significant morbidity and even death. [1-3]

The HPA axis is under circadian regulation and operates in a negative feedback loop to regulate cortisol secretion. The hypothalamus releases corticotrophin releasing hormone (CRH) which stimulates the pituitary gland to release adrenocorticotropic hormone (ACTH) which in turn stimulates the adrenal glands to secrete cortisol. Cortisol has inhibitory effects on both the release of CRH at the level of the hypothalamus and of ACTH at the level of the pituitary gland, in turn downregulating cortisol production and secretion. Exogenous glucocorticoids exert negative feedback at the level of the hypothalamus and pituitary gland, leading to a reduction in CRH and ACTH and in some cases adrenocortical hypoplasia or atrophy. These changes are associated with decreased cortisol production leading to adrenal insufficiency (AI). AI secondary to exogenous glucocorticoid exposure is also referred to as adrenal suppression. [3-5]

Adrenal suppression is the most common form of adrenal insufficiency amongst both children and adults.[6,7] Despite being a treatable condition, failure of adequate preventative measures or delayed treatment has led to unnecessary morbidity and death in individuals with AI including AS.[6-8]

Symptoms of AS are often non-specific (Table 1) and can go undetected until a physiologic stress (illness, surgery, injury) precipitates an adrenal crisis. [6] Adrenal crisis has also been reported in the absence of physiologic stress, likely secondary to unrecognized signs or symptoms of AS. [2,6] Symptomatic AS including adrenal crisis can be prevented by recognizing children at risk and administering physiologic GC replacement and/or higher doses of GCs during times of stress. [3,6]

A recent study evaluating the national incidence of symptomatic AS in children in Canada reported 46 cases including 6 (13%) cases of adrenal crisis over 2 years with 37/46 (80%) of children using ICS either alone or in combination with another form of GC.[8] Asymptomatic biochemical evidence of AS is considerably more frequent with nearly 100% of patients having AS immediately after discontinuation of high dose systemic therapy but significantly less frequent if measured after days or weeks or if exposed to other forms of GC therapy. [9-12]

Despite clear evidence of the morbidity associated with AS in the pediatric population, evidence-based guidelines about screening and management of children at risk are lacking. There are few known risk factors for the development of *symptomatic* AS, therefore the burden of screening for and managing asymptomatic biochemical AS needs to be balanced with the risk of severe morbidity and mortality in a subset of patients. There is a lack of consensus amongst pediatric endocrinologists about the approach to the management of children at risk of AS and as a result, clinicians who are prescribing GC therapy may have limited guidance about how to keep their patients safe. Within this review article, our working group comprised of pediatric endocrinologists, pediatricians and other pediatric subspecialists who frequently prescribe GC

therapy present the best available evidence about AS risk, screening, testing and management while acknowledging the controversies that exist about the management of AS. The intent of this review is to draw attention to this important entity and to allow the reader to create an informed and practical approach to the management of their patients at risk.

Adrenal suppression in children treated with systemic glucocorticoids

Both clinical and biochemical evidence of AS have been well described in children following discontinuation of therapeutic doses of systemic GCs.[10,12-14] Shorter term systemic GC exposure is associated with more transient AS. [15,16] In practice, exposure for greater than 2 weeks is used as a threshold for risk of clinically important AS. [6] Duration of AS following prolonged GC exposure has been reported to be up to 2 years. [9,12] Symptomatic AS including adrenal crisis and death are well documented related to systemic GC therapy.[3,8,13,17] Higher dose is a risk factor [18], while longer duration and timing of administration of GCs (evening vs. morning and daily vs. every other day) are theoretical risks. [18,19] [5]

We did not find literature exploring risk of repeated intermittent GC exposure.

Adrenal suppression in children treated for asthma with inhaled corticosteroids

Symptomatic AS associated with ICS use is rare but important and the risk can be reduced by using the lowest dose of ICS sufficient to maintain acceptable asthma control, as outlined in current asthma guidelines. [20-22]National asthma guidelines recommend consultation with asthma specialists if children or adolescents meet criteria for treatment with high (or moderate) dose ICS therapy.[22] [20,21]

There have been more than 90 case reports in the literature of adrenal crisis or death secondary to ICS use for the treatment of asthma. [1,23-25] Pharmacokinetic and pharmacodynamic properties and dose, in addition to ICS mode of delivery, play a role in the risk of AS[2] and therefore doses associated with increased risk of AS risk differ between medications (see Table 2). Clinicians can consider the use of high dose ICS therapy as defined by asthma guidelines as an important risk factor for AS, particularly because the current literature does not provide clear thresholds for AS risk. [8,11,20-22,26-28]An important exception to this rule is fluticasone, an ICS that has been associated with the majority of cases of symptomatic AS in doses of 500 µg daily or greater (500 µg is moderate dosing for children ≥ 12 years in some guidelines). [1,2,4,8,24,29,30] In addition, ciclesonide, a comparatively newer ICS, appears to have reduced AS risk[2,4,20,25,31,32] although cases of AS have been reported at high doses. [33]

While the majority of cases of symptomatic AS have been reported in children exposed to high dose ICS, there are rare reported cases of those receiving low to moderate dosing, [2,33] highlighting the importance of consideration of AS in children presenting with possible signs or symptoms of AS regardless of ICS dose. Conversely, while high dose ICS therapy increases the risk of AS, many children receiving high dose therapy are not suppressed [11]. A recent genome-wide association study suggests that a common genetic variant might lead to susceptibility to AS in patients exposed to ICS but further study is needed to support this finding.[34] There are also many genetic variants of the GC receptor gene which are thought to explain the wide inter-individual variation in GC sensitivity[5] and several single nucleotide polymorphisms that have been associated with HPA axis reactivity[3], both of which likely in part explain the variability in AS susceptibility. Other possible factors contributing to inter-patient variability in the

development of AS include inhaler technique, age and asthma severity which might impact both ICS deposition in the lungs and the amount of ICS absorbed into the systemic circulation.

In addition to high dose ICS therapy, exposure to courses of systemic GCs for treatment of asthma put children at risk of AS.[1,2,4,31] Achieving good asthma control with skilled use of controller therapy, including appropriately dosed ICS, will prevent exacerbations and reduce the need for long-term and/or repeated courses of GCs.[35] Other possible risk factors include concomitant intranasal corticosteroids, low BMI and cumulative glucocorticoid exposure.[2,8] Duration of ICS exposure has not been found to be a risk factor, however most studies have looked at exposures of 6 weeks or more. [34]

[3,5,11]Clinicians need to be aware of the ICS doses contained in combination inhalers and should consider those as increasing the risk of AS based on the ICS component (see Table 2).

Adrenal suppression in children treated with other forms of glucocorticoids

Studies of the risk of AS related to intranasal corticosteroids alone have had variable results although use in conjunction with ICS is a risk factor. [36,37,38]

While the use of low to moderate potency topical corticosteroids is rarely associated with a risk of AS[39], there have been case reports of symptomatic AS and cushingoid features in infants receiving potent topical GCs for >1 month with misuse of the medication.[40] Symptomatic AS associated with cushingoid features has also been reported with ocular GCs.[41] AS has been associated with intra-articular GCs in adults. [42]

Studies suggest that children receiving swallowed ICS for eosinophilic esophagitis or inflammatory bowel disease are at risk of AS.[8,43,44]

Medications potentiating systemic effects of glucocorticoids

CYP3A4 inhibitors, including several antiretroviral medications, antifungal agents and select antidepressants, prolong the biologic half-life of GCs. These medications have been reported (a) in several cases of symptomatic AS associated with relatively low doses of ICS, and (b) with a prolonged duration of AS following systemic GC exposure. [10,45,46]

Glucocorticoid taper

There is no evidence to support a specific approach to GC taper for the prevention of AS. [3,47] It has been demonstrated that a gradual GC taper does not prevent AS.[12] GCs should be tapered or discontinued at a rate dictated by the underlying condition in order to maintain disease remission; if not indicated for prevention of disease relapse, a prolonged taper should be avoided to prevent unnecessary GC exposure. Physiological GC replacement should prevent symptoms of AS,[6] so testing of the HPA axis prior to discontinuing or tapering GCs below a physiological dose (<8mg/m^2/day hydrocortisone equivalent) should be considered in children who have received prolonged courses of GCs (Table 5 -GC dose equivalencies). Symptoms of GC withdrawal can occur during a rapid taper and may mimic symptoms of AS despite biochemical evidence of HPA system integrity or adequate GC replacement. [48] Clinicians need to be aware of this possibility, evaluate for possible AS, and modify their taper accordingly.

Testing for adrenal suppression

Testing for adrenal insufficiency (AI), including AS, is a challenge for clinicians due to lack of standardization of cortisol assays and lack of clinical association with established cortisol

thresholds used for diagnosis.[49,50] Of particular note are newer generation assays including the Roche Cortisol II immunoassay which is reported to measure cortisol levels approximately 30% lower than the older Roche immunoassay.[51] Clinicians must be aware of the thresholds associated with the assay used in their local laboratory.

Cortisol thresholds cited within this section are reported from studies that have employed older generation immunoassays and as such, need to be interpreted with caution. First morning cortisol (7-9 am) is often used in screening for AI. A first morning cortisol is specific for diagnosis of AI if ≤100nmol/L (≤3.6μg/dL) in individuals with a normal sleep-wake cycle in whom GCs are withheld for *at least* 24 hours.[52,53] GCs with longer duration of action must be held for longer than 24 hours. Clinicians must assess the safety of discontinuing GC therapy for testing and modify their approach accordingly (see Table 3). Since cortisol production is under circadian regulation, a low morning cortisol is poorly predictive of AS in infants and children who do not have a regular sleep-wake cycle, and dynamic testing is indicated. [54] A first morning cortisol value of ≥ 350 - 500nmol/L (≥ 13-18μg/dL) can predict normal HPA axis function. [53,55,56] The Pediatric Endocrine Society Pharmacy and Therapeutics guideline about endocrine side effects of ICS suggests that a first morning cortisol value of 275nmol/L (10μg/dL) may be considered as a screening threshold in asymptomatic patients [2]. However, there is no single absolute cutoff for morning cortisol that can be used to confidently rule in or out AS.

Provocative testing is typically required for diagnosis of central AI including AS. Both standard dose (250μg) and low dose (1μg) ACTH stimulation tests are used in clinical practice for

evaluation of central AI with significant debate about which is superior, some studies suggesting that the low dose stimulation test (LDST) is significantly more sensitive but less specific with other studies not supporting this finding.[50,55,57] Peak cortisol thresholds of 440-600 nmol/L (16-22μg/dL) are commonly used to rule out AI but vary between studies and institutions since many factors must be considered when interpreting results (e.g., cortisol assay, timing of cortisol draws relative to corticotropin administration, medications affecting cortisol binding, time of day).[54,58,59] Clinicians must therefore refer to their local protocols for guidance. Appropriate preparation and procedures for testing of the HPA axis are required (See Table 3).

Glucocorticoid replacement

Cortisol production is significantly higher during physiological stress in healthy individuals. [60] Individuals with AI are at risk of adrenal crisis during illness, surgery or injury. Gastrointestinal illness is the most common precipitant of adrenal crisis.[61] In practice, stress dosing of GCs is provided during physiological stresses in order to prevent adrenal crisis in children with AI (Table 4). [13,17,62] There is currently insufficient data to recommend GC coverage during moderate-to-extreme activity or emotional stress. [6,63]

Hydrocortisone is the medication of choice for stress dosing, particularly during adrenal crisis because of its mineralocorticoid effect (Table 4).[61] However, in practice, while receiving active systemic GC therapy, stress dosing for moderate illness is often provided using the same form of GC that is being used to treat disease, rather than hydrocortisone (see Table 5 for relative potencies).

Children with symptomatic AS require daily physiologic GC replacement[2] (Table 4). Daily GC replacement is also an important consideration in children with clear biochemical evidence of AS[64], even in the absence of well-defined symptoms, but remains controversial among pediatric endocrinologists, with no literature supporting or refuting this approach. Hydrocortisone, with its short half-life, is the drug of choice for daily replacement with dosing of approximately 8mg/m^2/day considered to be physiological.[65,66] While three times daily (TID) hydrocortisone dosing is standard of care in primary AI,[66] many endocrinologists provide once or twice daily dosing in AS, with higher doses in the morning to reduce the ongoing suppression of endogenous morning cortisol production in *asymptomatic* patients. There is no evidence to support this approach but in practice, it is used by several members of our working group with the assumption that the AI in cases of asymptomatic AS is partial and that this approach will help to reduce the risk of prolonging suppression. Clinicians must be aware of the short half-life of hydrocortisone and provide BID or TID dosing if a child is symptomatic and during times of stress.[6,67,68]

Strong CYP3A4 inducers, such as phenobarbital, carbamazepine or rifampicin, may decrease the serum concentration of GCs requiring an awareness of the need for dose adjustment in the context of ongoing symptoms or poor response to stress dosing in the management of AS.[69,70]

How can we reduce the risk of AS and adrenal crisis?

Despite being largely preventable, morbidity and mortality associated with AS continue to be reported. We suggest that the following measures be considered to reduce this risk:

1. Clinician education and awareness about the risk of AS including an understanding of the relatively high frequency of AS in patients being treated with ≥ 500 mcg of fluticasone or high dose ICS therapy as defined by national or international asthma guidelines.

2. Clinicians should prescribe the lowest effective dose of GCs with regular re-evaluation. If once-daily GC dosing is appropriate, GCs should be given in the morning to minimize suppression of the HPA axis.

3. Families should be educated about the risk of AS with an understanding that the benefits of GC therapy outweigh the risks, and that medication adherence and clinical follow-up are the best preventative measures for symptomatic AS.

4. All children with possible signs or symptoms of AS, including poor growth, and with current or recent history of GC/ICS use should be tested for AS. Symptomatic children with biochemical evidence of AS should be treated with both physiological GC replacement and stress dosing GCs (Table 4).

5. Stress dosing should be provided for critical illness or major surgery, in all children being actively treated with GCs and should be *considered* in all children who have recently discontinued GC therapy (up to a year for those with prolonged exposure) unless they have been proven to have a normal HPA axis. Cortisol should be drawn prior to initiating stress dosing during a critical illness if the diagnosis of AS is not confirmed.

6. Screening of children at high risk of AS should be *considered*. An alternative approach may be to provide empiric stress dosing once GC doses are tapered to <30 mg/m^2/day of

hydrocortisone equivalent and for up to 6-12 months following GC discontinuation. There is no evidence to support a specific approach to asymptomatic children with AS.

7. Children with biochemical evidence of AS should receive stress dosing. Treatment with physiological GC dosing should be considered.

8. Families of children with proven or suspected AS should be educated about stress dosing (Table 4) and provided with a stress dosing card or handout outlining doses, indications for stress dosing and indications to seek emergency help. Wearing a medical alert identification should be considered.

9. Family/caregiver education for administration of intramuscular (IM) hydrocortisone for use during severe illness or when unable to tolerate oral therapy should be considered for all children with possible or proven AS, especially in those who live or travel remotely.

Conclusions

While relatively uncommon, symptomatic AS can be associated with significant morbidity and mortality. Symptomatic AS can be prevented by responsible GC prescribing and follow-up, recognition of signs and symptoms including poor growth, and screening and treatment of children at increased risk. Education of clinicians and at-risk patients/parents about AS is integral to reducing morbidity associated with this iatrogenic condition. Until further evidence is available, consultation with an endocrinologist should be considered when there is uncertainty about how to approach the management of a child or adolescent with possible or proven AS. Clinicians and families should not lose sight of the fact that GCs are essential for the

management of many pediatric conditions and that the risk of AS should not be a barrier to their use.

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Contributors statement:

AA led the development and coordination of the working group for the development of the review article, performed a literature review with the assistance of Victor Konji, wrote the initial draft of the manuscript, finalized edits submitted by authors and contributed her expertise as a pediatric endocrinologist.

AM, EG, CH and PK (pediatric endocrinologists) participated in teleconferences informing the content of the review article, reviewed and edited the manuscript and contributed their expertise as pediatric endocrinologists.

TK(pediatric respirologist), RJ(pediatric rheumatologist), and HK (allergist) participated in teleconferences informing the content of the review article, reviewed and edited the manuscript and contributed their expertise as sub-specialists who frequently prescribe glucocorticoids.

AR-L and LP participated in teleconferences informing the content of the review article, reviewed and edited the manuscript and contributed their expertise as general pediatricians who prescribe glucocorticoids to the recommendations.

All authors approved the final revised manuscript as submitted and agree to be accountable for all aspects of the work.

Table 1. Presenting symptoms and signs associated with Adrenal Suppression

Symptoms/Signs of Possible Adrenal Suppression
Poor linear growth*
Poor weight gain
Anorexia
Nausea/vomiting
Malaise
Weakness/fatigue
Headache
Abdominal pain
Myalgia/arthralgia
Psychiatric symptoms
Signs of Adrenal Crisis
Hypotension
Hypoglycemia (seizure/coma)
Signs Associated with Adrenal Suppression
Cushingoid features

*Poor linear growth has been reported in close to 50% of patients with symptomatic AS.[8] Table adapted from Ahmet et al 2011.[4]

Table 2. ICS type and doses associated with increased Adrenal Suppression risk[a]

Corticosteroid	Dose associated with increased AS risk [b] (µg/day) Canadian/European Dosing	Dose associated with increased AS risk [b] (µg/day) American Dosing
Beclomethasone dipropionate HFA [26]	>400	>320
Budesonide DPI [8,26] Budesonide and formoterol	≥800	≥800
Ciclesonide[c]	>400	>320
Fluticasone propionate [1,8,11] Fluticasone and salmeterol	≥500	≥440 (HFA) ≥500 (DPI)
Fluticasone furoate DPI [27]	≥100	≥100
Mometasone DPI [28] Mometasone formoterol	≥800	≥800

[a]Doses associated with increased risk of AS are based on the best available literature. Where no specific evidence for AS risk in pediatrics was available, doses cited are from adult studies with the exception of ciclesonide. Because of lack of clear thresholds for increased risk, we recommend that high dose therapy (as defined by national or international guidelines)[20-22], prompts the clinician to consider patients to be at increased risk recognizing that AS is possible even with low to moderate dosing.

[b] In the US, inhaler dose is based on the amount leaving the mouthpiece, rather than the amount leaving the canister, this accounts for differences in listed (but not actual) doses.

[c]While ciclesonide has been demonstrated to have reduced risk of systemic side effects, cases of AS have been reported with high doses[33]

[d]Fluticasone Furoate (Arnuity Ellipta and Breo Ellipta) contain a new potent ICS. 100µg daily is equivalent to 500µg daily of fluticasone. This formulation has a high potential risk for AS. [27]

Table 3. Tests of HPA axis function: Considerations for testing

Procedure	Considerations for testing

All Tests	• Hold all oral GCs prior to the test based on their duration of action[a]:
	  ○ hydrocortisone x 24 hours,
	  ○ prednisone x 48 hours,
	  ○ dexamethasone x 72 hours
	• Consideration of a switch to hydrocortisone prior to testing should be considered in children at high risk of AS[a]
	• Hold ICS the evening and morning prior to the test if patient stable [b]

First morning cortisol [c]	• 7-9 am test (Before 8 am is optimal) • Tests drawn after 9 am must be repeated if abnormal
Low dose ACTH stimulation[h]	• Perform test in the morning[71] • 1µg corticotropin analog [f;5] • Minimal tubing length for administration of corticotropin reduces the possibility of adherence to plastic tubing[71] • Cortisol drawn at 0, 15, 30 and 60 minutes for peak levels[g;58]
Standard dose ACTH stimulation	• 250µg[h] corticotropin analog • Cortisol drawn at 0, 30 and 60 minutes • Currently no evidence to support morning vs afternoon testing

[a]In some cases, it may be unsafe to hold medications for the duration required. Consideration of a wean to physiological hydrocortisone dosing may be made in some circumstances to facilitate testing and address safety concerns.

[b]In children where it is unsafe to hold evening ICS dose, abnormal cortisol levels must be interpreted with caution.
[c]In infants and children with disrupted sleep-wake cycles, an abnormal first morning cortisol is not diagnostic of AS. Provocative testing is indicated.
[d]Provocative testing is required to definitively rule in or out AS.
[f]Careful dilution and timely administration of corticotropin is required. [71]
[g]Protocols for Low Dose ACTH stimulation tests including timing of cortisol samples may vary between institutions.
[h]For infants: corticotropin dose =15µg/kg up to a maximum dose of 250µg

Table 4. Glucocorticoid replacement and stress dosing

Indication	**Glucocorticoid dose[a,b]**
Adrenal crisis, severe illness or severe injury	Hydrocortisone 100 mg/m^2 (max 100 mg) IV/IM stat, then 100 mg/m^2 (max 200 mg) divided q 6 hours or by continuous infusion
Major Surgery	Hydrocortisone 50-100 mg/m^2 IV (max 100 mg) pre-op, then 100 mg/m^2/24 hrs IV (max 200 mg) by continuous infusion or divided q 6 hrs
Minor to Moderate Surgery or procedure requiring general anesthesia	Hydrocortisone 50 mg/m^2 IV (max 100 mg) pre-op, then as indicated by clinical status (typically moderate illness dosing x 1-2 days)
Moderate Illness including fever ≥38.5^o, vomiting, diarrhea, severe head cold with fatigue or injury *Able to tolerate orally*	30 mg/m^2/day hydrocortisone equivalent[c] divided TID until resolution of symptoms Duration >3 days should be reassessed by the health care team[d]
Moderate Illness including fever ≥38.5^o, vomiting, diarrhea, severe head cold with fatigue or injury *Inability to tolerate orally*	Hydrocortisone must be given parenterally 30-50 mg/m^2/day hydrocortisone divided q 6 hourly IV or q 8 hourly IM Consult endocrinology to re-assess parenteral dose if the child is still unable to tolerate orally after 24 hours of parenteral administration
Severe illness or moderate illness and unable to tolerate orally BEFORE arriving in ED	Consider teaching administration of IM hydrocortisone in all patients with AS Families who do not have rapid access to a hospital ED or who are planning remote travel (airplane, camping, etc.) should be taught administration of IM hydrocortisone
Daily Physiologic Hydrocortisone Dosing	
8 mg/m^2/day hydrocortisone daily (divided BID-TID if symptomatic with higher dose in the morning)	

[a]Poor evidence for pediatric dosing. Recommendations based on expert opinion and best available evidence. [6,66-68]

[b]Dosing may need to be adjusted in children receiving CYP3A4 Inducers. Endocrinology should be consulted in these cases.

[c]In children on active therapy in doses ≥30 mg/m^2/day hydrocortisone equivalent (≥7.5mg/m^2/day prednisone), stress dosing for mild-moderate illness can be acheived by dividing the therapeutic prednisone dose to be given BID (i.e. therapeutic dose is sufficient for stress coverage). Once therapeutic GC is no longer needed, stress dosing should be provided using hydrocortisone.

[d]Frequent or prolonged duration of stress dosing can contribute to adrenal suppression. Stress dosing is not required for very mild symptoms such as a persistent runny nose.

Table 5. Relative glucocorticoid potencies[a]

	Anti-Inflammatory Potency	HPA Suppression Potency[b]	Duration of action (hours)
Hydrocortisone (cortisol)	1	1	8 to 12
Prednisone	4	4	12 to 36
Prednisolone	4	4	12 to 36
Methylprednisolone	5	5	12 to 36
Dexamethasone	30	50 (17-100)	36 to 72

[a]HPA suppression potencies should be used when calculating hydrocortisone equivalent doses for evaluation of AS risk

[b]Available data about relative HPA suppression potency is limited and widely variable. Studies of growth suppressive effects of prednisone, prednisolone, methylprednisolone and dexamethasone suggest that secondary effects on growth relative to anti-inflammatory effects may be significantly higher. References [72-74]

References:

1. Todd GR, Acerini CL, Ross-Russell R, Zahra S, Warner JT, McCance D. Survey of adrenal crisis associated with inhaled corticosteroids in the United Kingdom. Arch Dis Child 2002;87:457-61.
2. Kapadia CR, Nebesio TD, Myers SE, et al. Endocrine Effects of Inhaled Corticosteroids in Children. JAMA Pediatr 2016;170:163-70.
3. Dinsen S, Baslund B, Klose M, et al. Why glucocorticoid withdrawal may sometimes be as dangerous as the treatment itself. Eur J Intern Med 2013;24:714-20.
4. Ahmet A, Kim H, Spier S. Adrenal suppression: A practical guide to the screening and management of this under-recognized complication of inhaled corticosteroid therapy. Allergy Asthma Clin Immunol 2011;7:13.
5. Miller WLF, Christa E. In: Sperling MA, ed. Pediatric Endocrinology. Fourth Edition ed. Philadelphia, PA: Elsevier 2014:521-5.
6. Shulman DI, Palmert MR, Kemp SF. Adrenal insufficiency: still a cause of morbidity and death in childhood. Pediatrics 2007;119:e484-94.
7. Puar TH, Stikkelbroeck NM, Smans LC, Zelissen PM, Hermus AR. Adrenal Crisis: Still a Deadly Event in the 21st Century. Am J Med 2016;129:339 e1-9.
8. Goldbloom EB, Mokashi A, Cummings EA, et al. Symptomatic adrenal suppression among children in Canada. Arch Dis Child 2017;102:338-9.
9. Wildi-Runge S, Deladoey J, Belanger C, et al. A search for variables predicting cortisol response to low-dose corticotropin stimulation following supraphysiological doses of glucocorticoids. The Journal of pediatrics 2013;163:484-8.
10. Rensen N, Gemke RJ, van Dalen EC, Rotteveel J, Kaspers GJ. Hypothalamic-pituitary-adrenal (HPA) axis suppression after treatment with glucocorticoid therapy for childhood acute lymphoblastic leukaemia. Cochrane Database Syst Rev 2017;11:CD008727.
11. Smith RW, Downey K, Gordon M, et al. Prevalence of hypothalamic-pituitary-adrenal axis suppression in children treated for asthma with inhaled corticosteroid. Paediatr Child Health 2012;17:e34-9.
12. Ahmet A, Brienza V, Tran A, et al. Frequency and Duration of Adrenal Suppression Following Glucocorticoid Therapy in Children With Rheumatic Diseases. Arthritis Care Res (Hoboken) 2017;69:1224-30.
13. Einaudi S, Bertorello N, Masera N, et al. Adrenal axis function after high-dose steroid therapy for childhood acute lymphoblastic leukemia. Pediatr Blood Cancer 2008;50:537-41.
14. Bowden SA, Connolly AM, Kinnett K, Zeitler PS. Management of Adrenal Insufficiency Risk After Long-term Systemic Glucocorticoid Therapy in Duchenne Muscular Dystrophy: Clinical Practice Recommendations. J Neuromuscul Dis 2019;6:31-41.
15. Zora JA, Zimmerman D, Carey TL, O'Connell EJ, Yunginger JW. Hypothalamic-pituitary-adrenal axis suppression after short-term, high-dose glucocorticoid therapy in children with asthma. J Allergy Clin Immunol 1986;77:9-13.
16. Henzen C, Suter A, Lerch E, Urbinelli R, Schorno XH, Briner VA. Suppression and recovery of adrenal response after short-term, high-dose glucocorticoid treatment. Lancet 2000;355:542-5.
17. Rix M, Birkebaek NH, Rosthoj S, Clausen N. Clinical impact of corticosteroid-induced adrenal suppression during treatment for acute lymphoblastic leukemia in children: a prospective observational study using the low-dose adrenocorticotropin test. The Journal of pediatrics 2005;147:645-50.
18. Hawcutt DB, Jorgensen AL, Wallin N, et al. Adrenal responses to a low-dose short synacthen test in children with asthma. Clinical endocrinology 2015;82:648-56.

19. Adam HM. Fever and host responses. Pediatr Rev 1996;17:330-1.
20. Lougheed MD, Lemiere C, Ducharme FM, et al. Canadian Thoracic Society 2012 guideline update: diagnosis and management of asthma in preschoolers, children and adults. Can Respir J 2012;19:127-64.
21. National Asthma Education and Prevention Program (NAEPP). Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. National Heart, Lung and Blood Institute 2007. . (Accessed September 22, 2019, at https://www.nhlbi.nih.gov/files/docs/guidelines/asthgdln.pdf.)
22. Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. . (Accessed September 18, 2019, at www.ginasthma.org.)
23. Donaldson MD, Morrison C, Lees C, et al. Fatal and near-fatal encephalopathy with hyponatraemia in two siblings with fluticasone-induced adrenal suppression. Acta Paediatr 2007;96:769-72.
24. Schwartz RH, Neacsu O, Ascher DP, Alpan O. Moderate dose inhaled corticosteroid-induced symptomatic adrenal suppression: case report and review of the literature. Clinical pediatrics 2012;51:1184-90.
25. Heller MK, Laks J, Kovesi TA, Ahmet A. Reversal of adrenal suppression with ciclesonide. J Asthma 2010;47:337-9.
26. Ninan TK, Reid IW, Carter PE, Smail PJ, Russell G. Effects of high doses of inhaled corticosteroids on adrenal function in children with severe persistent asthma. Thorax 1993;48:599-602.
27. Lotvall J, Bleecker ER, Busse WW, et al. Efficacy and safety of fluticasone furoate 100 mug once-daily in patients with persistent asthma: a 24-week placebo and active-controlled randomised trial. Respir Med 2014;108:41-9.
28. Fardon TC, Lee DK, Haggart K, McFarlane LC, Lipworth BJ. Adrenal suppression with dry powder formulations of fluticasone propionate and mometasone furoate. Am J Respir Crit Care Med 2004;170:960-6.
29. Zollner EW. Hypothalamic-pituitary-adrenal axis suppression in asthmatic children on inhaled corticosteroids (Part 2)--the risk as determined by gold standard adrenal function tests: a systematic review. Pediatr Allergy Immunol 2007;18:469-74.
30. Patel L, Wales JK, Kibirige MS, Massarano AA, Couriel JM, Clayton PE. Symptomatic adrenal insufficiency during inhaled corticosteroid treatment. Arch Dis Child 2001;85:330-4.
31. Lipworth BJ, Kaliner MA, LaForce CF, et al. Effect of ciclesonide and fluticasone on hypothalamic-pituitary-adrenal axis function in adults with mild-to-moderate persistent asthma. Ann Allergy Asthma Immunol 2005;94:465-72.
32. Liddell BS, Oberlin JM, Hsu DP. Inhaled corticosteroid related adrenal suppression detected by poor growth and reversed with ciclesonide. J Asthma 2017;54:99-104.
33. Cavkaytar O, Vuralli D, Arik Yilmaz E, et al. Evidence of hypothalamic-pituitary-adrenal axis suppression during moderate-to-high-dose inhaled corticosteroid use. Eur J Pediatr 2015;174:1421-31.
34. Hawcutt DB, Francis B, Carr DF, et al. Susceptibility to corticosteroid-induced adrenal suppression: a genome-wide association study. Lancet Respir Med 2018;6:442-50.
35. Guilbert TW, Morgan WJ, Zeiger RS, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. The New England journal of medicine 2006;354:1985-97.
36. Patel D, Ratner P, Clements D, Wu W, Faris M, Philpot E. Lack of effect on adult and adolescent hypothalamic-pituitary-adrenal axis function with use of fluticasone furoate nasal spray. Ann Allergy Asthma Immunol 2008;100:490-6.
37. Skoner DP, Berger WE, Gawchik SM, Akbary A, Qiu C. Intranasal triamcinolone and growth velocity. Pediatrics 2015;135:e348-56.

38. Zollner EW, Lombard C, Galal U, Hough S, Irusen E, Weinberg E. Hypothalamic-pituitary-adrenal axis suppression in asthmatic children on inhaled and nasal corticosteroids--more common than expected? J Pediatr Endocrinol Metab 2011;24:529-34.
39. Wood Heickman LK, Davallow Ghajar L, Conaway M, Rogol AD. Evaluation of Hypothalamic-Pituitary-Adrenal Axis Suppression following Cutaneous Use of Topical Corticosteroids in Children: A Meta-Analysis. Horm Res Paediatr 2018;89:389-96.
40. Bulus AD, Andiran N, Kocak M. Cushing's syndrome: hidden risk in usage of topical corticosteroids. J Pediatr Endocrinol Metab 2014;27:977-81.
41. Chiang MY, Sarkar M, Koppens JM, Milles J, Shah P. Exogenous Cushing's syndrome and topical ocular steroids. Eye (Lond) 2006;20:725-7.
42. Johnston PC, Lansang MC, Chatterjee S, Kennedy L. Intra-articular glucocorticoid injections and their effect on hypothalamic-pituitary-adrenal (HPA)-axis function. Endocrine 2015;48:410-6.
43. Ahmet A, Benchimol EI, Goldbloom EB, Barkey JL. Adrenal suppression in children treated with swallowed fluticasone and oral viscous budesonide for eosinophilic esophagitis. Allergy Asthma Clin Immunol 2016;12:49: eCollection 2016.
44. Cohen SA, Aloi M, Arumugam R, et al. Enteric-coated budesonide for the induction and maintenance of remission of Crohn's disease in children. Curr Med Res Opin 2017;33:1261-8.
45. Foisy MM, Yakiwchuk EM, Chiu I, Singh AE. Adrenal suppression and Cushing's syndrome secondary to an interaction between ritonavir and fluticasone: a review of the literature. HIV medicine 2008;9:389-96.
46. Bornstein SR. Predisposing factors for adrenal insufficiency. The New England journal of medicine 2009;360:2328-39.
47. Richter B, Neises G, Clar C. Glucocorticoid withdrawal schemes in chronic medical disorders. A systematic review. Endocrinology and metabolism clinics of North America 2002;31:751-78.
48. Dixon RB, Christy NP. On the various forms of corticosteroid withdrawal syndrome. Am J Med 1980;68:224-30.
49. Hawley JM, Owen LJ, Lockhart SJ, et al. Serum Cortisol: An Up-To-Date Assessment of Routine Assay Performance. Clin Chem 2016;62:1220-9.
50. Ng SM, Agwu JC, Dwan K. A systematic review and meta-analysis of Synacthen tests for assessing hypothalamic-pituitary-adrenal insufficiency in children. Arch Dis Child 2016;101:847-53.
51. Kline GA, Buse J, Krause RD. Clinical implications for biochemical diagnostic thresholds of adrenal sufficiency using a highly specific cortisol immunoassay. Clin Biochem 2017;50:475-80.
52. Maguire AM, Biesheuvel CJ, Ambler GR, Moore B, McLean M, Cowell CT. Evaluation of adrenal function using the human corticotrophin-releasing hormone test, low dose Synacthen test and 9am cortisol level in children and adolescents with central adrenal insufficiency. Clinical endocrinology 2008;68:683-91.
53. Le Roux CW, Meeran K, Alaghband-Zadeh J. Is a 0900-h serum cortisol useful prior to a short synacthen test in outpatient assessment? Ann Clin Biochem 2002;39:148-50.
54. Kazlauskaite R, Maghnie M. Pitfalls in the diagnosis of central adrenal insufficiency in children. Endocr Dev 2010;17:96-107.
55. Kazlauskaite R, Evans AT, Villabona CV, et al. Corticotropin tests for hypothalamic-pituitary-adrenal insufficiency: a metaanalysis. The Journal of clinical endocrinology and metabolism 2008;93:4245-53.
56. Woods CP, Argese N, Chapman M, et al. Adrenal suppression in patients taking inhaled glucocorticoids is highly prevalent and management can be guided by morning cortisol. European journal of endocrinology / European Federation of Endocrine Societies 2015;173:633-42.

57. Ospina NS, Al Nofal A, Bancos I, et al. ACTH Stimulation Tests for the Diagnosis of Adrenal Insufficiency: Systematic Review and Meta-Analysis. The Journal of clinical endocrinology and metabolism 2016;101:427-34.
58. Gill H, Barrowman N, Webster R, Ahmet A. Evaluating the Low-Dose ACTH Stimulation Test in Children: Ideal Times for Cortisol Measurement. The Journal of clinical endocrinology and metabolism 2019;104:4587-93.
59. Park J, Didi M, Blair J. The diagnosis and treatment of adrenal insufficiency during childhood and adolescence. Arch Dis Child 2016;101:860-5.
60. Salem M, Tainsh RE, Jr., Bromberg J, Loriaux DL, Chernow B. Perioperative glucocorticoid coverage. A reassessment 42 years after emergence of a problem. Ann Surg 1994;219:416-25.
61. Oprea A, Bonnet NCG, Polle O, Lysy PA. Novel insights into glucocorticoid replacement therapy for pediatric and adult adrenal insufficiency. Ther Adv Endocrinol Metab 2019;10:2042018818821294.
62. Hahner S, Spinnler C, Fassnacht M, et al. High incidence of adrenal crisis in educated patients with chronic adrenal insufficiency: a prospective study. The Journal of clinical endocrinology and metabolism 2015;100:407-16.
63. Weise M, Drinkard B, Mehlinger SL, et al. Stress dose of hydrocortisone is not beneficial in patients with classic congenital adrenal hyperplasia undergoing short-term, high-intensity exercise. The Journal of clinical endocrinology and metabolism 2004;89:3679-84.
64. Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy, asthma, and clinical immunology : official journal of the Canadian Society of Allergy and Clinical Immunology 2013;9:30.
65. Linder BL, Esteban NV, Yergey AL, Winterer JC, Loriaux DL, Cassorla F. Cortisol production rate in childhood and adolescence. The Journal of pediatrics 1990;117:892-6.
66. Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. The Journal of clinical endocrinology and metabolism 2016;101:364-89.
67. Bancos I, Hahner S, Tomlinson J, Arlt W. Diagnosis and management of adrenal insufficiency. The lancet Diabetes & endocrinology 2015;3:216-26.
68. Charmandari E, Nicolaides NC, Chrousos GP. Adrenal insufficiency. Lancet 2014;383:2152-67.
69. Borcherding SM, Baciewicz AM, Self TH. Update on rifampin drug interactions. II. Arch Intern Med 1992;152:711-6.
70. Lexicomp. Lexicomp Online. Wolters Kluwer; 2016.
71. Wade M, Baid S, Calis K, Raff H, Sinaii N, Nieman L. Technical details influence the diagnostic accuracy of the 1 microg ACTH stimulation test. European journal of endocrinology / European Federation of Endocrine Societies 2010;162:109-13.
72. Treatment of adrenal insufficiency in children. UpToDate. Wolters Kluwer, 2016. (Accessed 13 October, 2016, at https://www.uptodate.com/index.html#!/contents/treatment-of-adrenal-insufficiency-in-children?source=search_result&search=glucocorticoid%20potency&selectedTitle=6~7.)
73. Punthakee Z, Legault L, Polychronakos C. Prednisolone in the treatment of adrenal insufficiency: a re-evaluation of relative potency. The Journal of pediatrics 2003;143:402-5.
74. Chrousos, Pavlaki AN, Magiakou MA. Glucocorticoid Therapy and Adrenal Suppression [Updated 2011 Jan 11]. In: De Groot LJ, Chrousos G, Dungan K, et al., eds. South Dartmouth (MA); Available from: https://www.ncbi.nlm.nih.gov/books/NBK279156/: Endotext [Internet]; 2011.