

DRAFT - CPS POSITION STATEMENT

Adrenal Suppression from Glucocorticoids: Prevention, screening and management

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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

Symptoms of AS are often non-specific (Table 1) and can go undetected until a physiologic stress (illness, surgery, injury) precipitates an adrenal crisis⁴. Adrenal crisis has also been reported in the absence of physiologic stress, likely secondary to unrecognized symptoms of AS.^{2,4} Symptomatic AS including adrenal crisis can be prevented by recognizing children at risk and administering physiological GCs, and/or higher doses of GCs during times of stress.^{3,4} Despite being a treatable condition, failure of adequate preventive measures or delayed treatment has led to unnecessary morbidity and death in individuals with adrenal insufficiency (AI). Recognition of the risks for the development of adrenal crisis and patient education are key elements to its prevention.

A recent CPSP study, looking at the national incidence of symptomatic AS in children, reported 46 cases including 6 (13%) cases of adrenal crisis over 2 years with over 50% in children using ICS.⁵ Asymptomatic biochemical evidence of AS is considerably more frequent.⁶⁻⁹ AS is the most common form of AI in children.⁴

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. The lack of evidence for a uniform approach to screening and treatment of AS is a challenge for pediatricians and endocrinologists. We therefore formed a working group composed of community pediatricians, pediatric endocrinologists from across Canada and pediatric subspecialists to develop a joint CPS / Canadian Pediatric Endocrine Group (CPEG) statement.

This position statement gives an overview of the available evidence and provides recommendations for the practicing pediatrician that aim to provide a safe, practical approach to screening and management of patients at risk. Our working group acknowledges that the approach to adrenal suppression differs, even amongst members of the Canadian Pediatric Endocrine Group and there may be alternative reasonable approaches to this clinical problem.

Adrenal suppression in children treated with systemic glucocorticoids

Both clinical and biochemical evidence of AS has been well described in children following discontinuation of therapeutic doses of systemic GC.^{7,9-12} Shorter term systemic GC exposure is associated with transient AS,^{13,14} in practice, exposure for >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 1-2 years.^{6,9} Symptomatic AS including adrenal crisis and death are well documented related to systemic GC therapy.^{3,5,11,15} Higher dose, longer duration and timing of administration of GCs (evening > morning) are theoretical risks.^{16,17} To our knowledge, there is no literature exploring cumulative risk of repeated intermittent systemic GC exposure.

Glucocorticoid Taper

There is no evidence to support a specific approach to GC taper for the prevention of AS.^{3,18} It has been demonstrated that a gradual GC taper does not prevent AS.⁹ 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 this threshold should be done in children who have received prolonged courses of GCs (Algorithm 3). Symptoms of GC withdrawal can occur during a rapid taper and may mimic symptoms of AS.¹⁹ Clinicians need to be aware of this possibility, evaluate for possible AS, and modify their taper accordingly.

Adrenal suppression in children treated for asthma with inhaled corticosteroids

Inhaled corticosteroid (ICS) therapy is first-line asthma treatment in children, with well-proven efficacy. ICS therapy, when used according to current guidelines,²⁰ is rarely associated with clinically significant AS. The Canadian Thoracic Society Guidelines recommend high doses of ICS only be used by asthma specialists.²⁰

There have been greater than 90 case reports in the literature of adrenal crisis or death secondary to ICS use for the treatment of asthma.^{1,21-23} The majority of cases have been reported in children receiving 500 mcg or greater of fluticasone daily, although there have been reports with lower doses and other forms of ICS.^{1,2,5,10,22,24,25}

Pharmacokinetic and pharmacodynamic properties and dose, in addition to ICS mode of delivery, play a role in the risk of AS² (Table 2: Comparative ICS dosing²⁰ and recommended screening thresholds for AS). Important risk factors for the development of AS in children with asthma include frequent or prolonged courses of systemic GCs and use of high dose ICS either alone or in combination.^{1,2,10,26,27} 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 course of GCs.²⁸ Other possible risk factors for AS in children treated for asthma include concomitant intranasal corticosteroids, low BMI and cumulative ICS.² Duration of ICS exposure has not been found to be a risk factor, however the majority of studies have looked at exposures of 6 weeks or more.^{8,29}

Evidence of AS has been demonstrated with all forms of ICS (with the exception of ciclesonide) with greater risk associated with higher doses.^{23,26,30,31} Ciclesonide is a relatively new ICS that appears to have reduced AS risk^{23,26,2}. Recommended screening thresholds are generally equivalent to high dose therapy according to the Canadian Asthma Guidelines. Clinicians need to be aware of the ICS doses contained in combination inhalers and should screen based on the ICS component, according to the recommendations contained in 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.^{32,33} The use of intranasal corticosteroids in conjunction with ICS has been shown to be a risk factor for AS.³⁴

There have been case reports of symptomatic AS and cushingoid features in infants receiving potent topical GCs for >1 month duration with misuse of the medication.³⁵ Symptomatic AS associated with cushingoid features has also been reported with ocular GCs.³⁶ AS has been associated with intra-articular GCs in adults.^{37,38}

AS has been clearly demonstrated in children receiving swallowed ICS for eosinophilic esophagitis.^{5,39} Recent studies suggest children with inflammatory bowel disease treated with swallowed ICS may also be at risk for AS.⁴⁰

Medications Potentiating Systemic Effects of Glucocorticoids

CYP3A4 inhibitors, including several HIV drugs, antifungal agents and select antidepressants, prolong the biologic half-life of GCs. These drugs have been reported a) in several cases of symptomatic AS associated with relatively low doses of ICS and b) to prolong duration of AS in systemic GC exposure.^{7,10,41-43}

Testing for adrenal suppression

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 in individuals with a normal sleep-wake cycle in whom GCs are withheld for at least 24 hours.^{44,45} Because 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.⁴⁶ A first morning cortisol value of $\geq 350 - 500$ nmol/L, can predict normal HPA axis function.^{45,47,48} From a practical perspective a first morning cortisol value of 275nmol/L has been used as a screening threshold in asymptomatic patients.²

Our working group recommends the low-dose ACTH stimulation test (LDST), 1 microgram, as the best available provocative test for the evaluation of AS in children but acknowledges that the standard dose (250 microgram) ACTH stimulation test is a reasonable alternative.^{16,47} A peak cortisol threshold of >500 nmol/L is commonly used to rule out AI but peak cortisol values vary between studies and institutions and this threshold has not been correlated with clinical symptoms or risk of adrenal crisis.¹⁶ We recognize that stimulation testing may not always be easily accessible.

While standard cortisol thresholds for diagnosis of AI are used throughout this statement, a lack of assay standardization and other factors contributing to measurement variability should raise caution for interpretation of “borderline” cortisol values.⁴⁶ Thresholds quoted in this statement are based on the best available literature and expert opinion and may not apply to all assays.

See Table 3: Tests of HPA axis function, for testing procedures.

Glucocorticoid replacement

Children with symptomatic AS require daily physiologic GC replacement (Table 4). Daily GC replacement is also an important consideration in high risk children with abnormal first morning cortisol even in the absence of clear symptoms but remains controversial among pediatric endocrinologists. Our working group advocates for the use of daily GC replacement because: a) reports of adrenal crisis are not always associated with intercurrent illness,⁵ therefore stress dosing alone will not necessarily prevent morbidity, b) symptoms of AI are non-specific and may be missed by physicians or families, and c) there are cases of adrenal crisis in children who are actively receiving high dose ICS therapy indicating that systemic absorption is not always sufficient⁵

Evaluation of possible AS and administration of daily GC replacement in children receiving systemic GC therapy, *is only indicated once therapeutic doses of GCs have been discontinued or tapered to less than a physiological dose (< 8 mg/m²/day hydrocortisone equivalent)*. Hydrocortisone, with its short half-life, is the drug of choice because it allows for finer titration and is best able to mimic physiologic cortisol secretion. While TID hydrocortisone dosing is standard of care in primary AI,⁴⁹ many endocrinologists provide BID dosing in AS, with higher doses in the morning to more closely mimic circadian regulation and to reduce the suppression of endogenous morning cortisol production. Some clinicians choose to provide hydrocortisone as once daily dosing first thing in the morning, when first morning cortisol is above 100 nmol/L. Clinicians must be aware of the short half-life of hydrocortisone and consider TID dosing if a child remains symptomatic.^{4,50,51} There are no studies comparing hydrocortisone dosing regimens in AS.

Cortisol production is significantly higher during physiological stress in healthy individuals.⁵² Children with proven or suspected AS should receive stress doses of GCs during stress (surgery, illness, injury), to prevent the risk of adrenal crisis (table 4).^{11,15,53,54} There is currently insufficient data to recommend GC coverage during moderate-to-extreme activity or emotional stress.^{4,55,56}

While receiving active systemic GC therapy, stress dosing for mild to moderate illness can be provided using the therapeutic GCs rather than hydrocortisone (see Table 5 for relative potencies). Stress dosing for severe illness however needs to be given parenterally using hydrocortisone, even while on active therapy (Table 4, Table 5). Once therapeutic GC is no longer needed for the underlying condition, stress dosing should be provided as hydrocortisone.

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. ^{57,58}

Recommendations

General considerations

- Symptomatic AS including adrenal crisis while rare, is a serious potential adverse effect of both systemic and inhaled GC therapy
- Despite the potential side effect of AS, ICS therapy when used according to current guidelines and short courses of systemic GC therapy are rarely associated with clinically significant AS
- There is currently poor evidence for a uniform screening and management approach. These recommendations are based on the best available evidence and expert opinion. Our working group acknowledges that there may be other reasonable approaches to management

How should we reduce the risk of AS?

- For the large majority of patients, clinician awareness of the potential of AS, reduction of AS risk and recognition of possible symptoms are the best preventative measures. However, closer attention to those at increased risk is required
- Clinicians should use the lowest effective dose of GC with regular re-evaluation
- Once-daily GC dosing should be administered in the morning when possible to minimize suppression of the HPA axis
- In most cases, GC taper can be guided by the underlying condition. Clinicians need to be aware of symptoms of possible AS or GC withdrawal and modify the taper accordingly (Algorithm 3)

How should we prevent morbidity related to AS?

- Clinicians should be aware of the signs and symptoms of possible AS (Table 1), including poor growth
- 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. See CPS patient handout [AA1](
- Families of children with proven or possible AS should be educated about stress dosing (Table 4) and provided with a stress dosing card (Appendix 2) or handout outlining doses, indications for

stress dosing and indications to seek emergency help. Consideration of a medical alert bracelet should be made

- Stress dosing should be provided for critical illness for all children being actively treated with GCs and should be *considered* in all children who have had discontinuation of GC therapy during the previous year 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
- During critical illness or injury, rapid administration of parenteral hydrocortisone is essential. In some provinces, paramedics will be able to administer the patient's own supply of intramuscular (IM) hydrocortisone. We strongly support the initiative to standardize EMS protocols across Canada with respect to administration of emergent GC therapy in individuals with AI including AS

Who should be screened/tested for AS?

- All children with current or recent history of GC/ICS use presenting with symptoms of adrenal crisis (hypoglycemia/altered mental status or severe hypotension) should be urgently evaluated and treated for possible AS
- All children with possible signs or symptoms of AS and with current or recent history of GC/ICS use (Table 1)
- We recommend routine screening in all children with the following risk factors:
 - Supra-physiological doses of systemic GCs for > 2 weeks (consecutive)
 - Threshold doses of ICS for ≥ 3 months (Table 2)
 - Swallowed ICS therapy (e.g. eosinophilic esophagitis, inflammatory bowel disease, graft vs host disease) for >1 month. *Follow algorithm 3*
 - Unexplained poor linear growth over a 6 month period AND treatment with any form of GCs over the past year or current treatment with non-systemic GCs
 - Treatment with non-systemic GCs who present with symptoms/signs of Cushing's syndrome
 - *Intermittent* supra-physiological doses of systemic GCs for ≥3 **cumulative** weeks in 3 months. *Follow algorithm 2 if 3-4 weeks cumulative exposure, algorithm 3 if >4 weeks cumulative exposure*
 - ICS of any dose in conjunction with CYP3A4 inhibitors for >3 months

How should we screen/test for adrenal suppression (see algorithm 1- 3)?

- When receiving a treatment course of systemic GCs, evaluation of the HPA axis should only be performed once **GC is no longer supraphysiologic** (Algorithm 2- 3)
- A first morning cortisol can be used as a screening tool for the detection of AS in patients at risk, although first morning cortisol thresholds for diagnosis are poorly defined
- A first morning cortisol of >275 nmol/L has been used empirically to identify a low risk of clinically significant AS
- The LDST should be used to definitely rule in or out AS
- The standard dose ACTH stimulation test is a reasonable alternative to the LDST in the evaluation of children with possible AS
- Glucocorticoids, including ICS should be held for 24 hours prior to any test of the HPA axis. If not possible, results should be interpreted with caution
- *See Algorithm 1-4 for screening and management of children at greatest risk (as listed in the section “who should be screened/tested for AS”)*

How should we manage children with possible or proven AS?

- Children with proven *symptomatic* AS should receive both daily physiological and stress dosing GCs
- Children with possible or proven *asymptomatic* AS should receive stress dosing and education about this
- While there is a lack of consensus amongst pediatric endocrinologists about the use of daily GC therapy in *asymptomatic* AS, our working group advocates for daily GC administration based on risk and morning cortisol threshold (Algorithm 1- 3)
- Physiological GC therapy, when indicated, should be provided preferentially as hydrocortisone at a dose of 8 mg/m²/day. BID dosing with a higher dose in the morning is indicated for most children however possible indications for once daily and TID dosing are outlined in table 4
- Teaching of IM hydrocortisone therapy 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 biochemical AS is relatively common in children treated with GC therapy, symptomatic AS is less frequently seen. Symptomatic AS can be prevented by responsible GC prescribing and follow-up, education about risks, recognition of signs and symptoms including poor growth, and screening and treatment of children at greatest risk. Uncertainty about management and in specific clinical contexts warrants consultation with endocrinology (Appendix 1). 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.

Appendix 1 – Tables and Figures (Online only)

Table 1 – Presenting symptoms and signs associated with AS

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 AS Cushingoid features

*Poor linear growth has been reported in close to 50% of patients with symptomatic AS (Goldbloom et al. 2016). ⁵Table adapted from Ahmet et al 2011.¹⁰

Table 2 –Comparative inhaled corticosteroids (ICS) dosing categories defined by the 2012 Canadian Asthma Guidelines and recommended screening thresholds for Adrenal Suppression

Corticosteroid	Trade Name	Daily ICS dose, mcg							
		Pediatric (6 to 11 years of age)				Adult (12 years of age and over)			
		Low	Moderate	High	Screening threshold ¹	Low	Moderate	High	Screening threshold ¹
Beclomethasone dipropionate HFA ⁵⁹	QVAR	≤200	201-400	>400	≥400	≤250	251-500	>500	≥400
Budesonide ⁵⁹	Pulmicort	≤400	401-800	>800	≥800	≤400	401-800	>800	≥800
Budesonide and formoterol	Turbuhaler Symbicort								
Ciclesonide	Alvesco	≤200	201-400	>400	>400	≤200	201-400	>400	>400
Fluticasone propionate ^{1,5,8}	Flovent MDI and spacer; Flovent Diskus;	≤200	201-400	>400	>400	≤250	251-500	>500	≥500
Fluticasone and salmeterol	Advair								
Fluticasone furoate ⁶⁰	Arnuity Ellipta* ⁶⁰ Breo Ellipta*				≥100mcg				≥100mcg
Mometasone ^{61,62}	Asmanex Twisthaler				>400mcg	200	≥400-800	>800	≥800
Mometasone formoterol	Zenhale								

*Arnuity Ellipta and Breo Ellipta (fluticasone furate) contain a new potent ICS. 100mcg daily is equivalent to 250mcg BID of fluticasone. This formulation has a high potential risk for AS.⁶⁰

Table 3: Tests of HPA Axis Function

Procedure	Considerations for testing	Cortisol Results ^a
All Tests	- Hold all oral GCs for 24 hours prior to the test - 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	< 100 nmol/L = AS likely ^{b,c,e; 2,44,45} 100-275 nmol/L = possible AS^{c; 3} >275 nmol/L = clinically significant AS unlikely² >500 nmol/L ⁴⁵ = no AS^a
Low dose ACTH stimulation ^h	- Perform test in the morning⁶³ 1 mcg corticotropin analog ^{f;5} - Minimal tubing length for administration of corticotropin reduces the possibility of adherence to plastic tubing⁶³ - Cortisol drawn at 0, 15, 30 and 60 minutes for peak levels^{i; 64}	<500 nmol/L = AS^g ≥500 nmol/L ^{45,47} = no AS^a

^aCortisol reference ranges differ between assays ⁶⁵. The thresholds quoted may not apply to all immunoassay platforms. Consult your local endocrinologist if there is uncertainty about the use of these thresholds.

^bIn children where it is unsafe to hold evening ICS dose, abnormal cortisol levels must be interpreted with caution.

^cIn infants and children with disrupted sleep-wake cycles, an abnormal first morning cortisol is not diagnostic of AS. Provocative testing is indicated. Referral to endocrinology should be considered for children <2 years of age or those with disrupted sleep-wake cycles.

^dProvocative testing is required to definitively rule in or out AS.

^eIn children with higher pre-test probability of AS (longer duration of GCs), we use a threshold of <150nmol/L to define likely AS (algorithm 2-3)

^fCareful dilution and timely administration of cortrosyn is required ⁶³

^gWhile a cortisol threshold of <500 nmol/L is often used to define adrenal insufficiency, borderline results (440-500nmol/L) should be considered with caution as this threshold is not 100% specific⁴⁷.

^hStandard dose ACTH stimulation tests (250 micrograms) are used in some institutions and are a reasonable alternative to the Low dose ACTH stimulation test.

ⁱProtocols for Low Dose ACTH stimulation tests including timing of cortisol may vary between institutions.

Table 4 : Glucocorticoid replacement and Stress Dosing

Indication	Glucocorticoid dose ^{1,4}
Adrenal crisis, severe illness or 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
Surgery	Hydrocortisone 50-100 mg/m ² IV (max 100 mg) pre-op, then 100 mg/m ² /24 hrs IV (max 100 mg) by continuous infusion or divided q 6 hrs
Moderate illness including Fever ≥38.5°, vomiting, diarrhea, lethargy, severe head cold or injury <i>Able to tolerate orally</i>	30 mg/m ² /day hydrocortisone equivalent ² divided TID until resolution of symptoms. Duration >3 days should be reassessed by the health care team ³ .
Vomiting or moderate illness and <i>unable to tolerate orally</i>	Must be given parenterally 25 mg/m ² /dose hydrocortisone 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 ER	Consider teaching administration of IM hydrocortisone in all patients with AS Families who do not have rapid access to a hospital ER or who are planning remote travel (airplane, camping, etc.) should be taught administration of IM hydrocortisone
Daily Physiologic Dosing	
- Children with symptomatic AS <i>Consider</i>⁶ in children with first morning cortisol <150 nmol/L post discontinuation of GCs <i>Consider</i>⁶ in children with first morning cortisol <100 nmol/L while on active	8 mg/m²/day hydrocortisone divided BID (higher dose in morning).⁵ Treatment should continue until normalization of the first morning cortisol (or evidence of a normal low dose ACTH stimulation test) Consider TID dosing if symptomatic or less than 2 years of age Consider once daily dosing if asymptomatic and cortisol >100 nmol/L

high dose ICS therapy	
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¹Poor evidence for pediatric dosing. Recommendations based on expert opinion and best available evidence. ^{4,49-51}

²In children on active therapy in doses $\geq 30 \text{ mg/m}^2/\text{day}$ hydrocortisone equivalent ($\geq 7.5 \text{ mg/m}^2/\text{day}$ prednisone), stress dosing for mild-moderate illness can be achieved 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.

³Frequent 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. In children with "possible AS" requiring frequent stress dosing, provocative testing to confirm the diagnosis, or referral to an endocrinologist is indicated.

⁴Dosing may need to be adjusted in children receiving CYP3A4 Inducers. Endocrinology should be consulted in these cases.

⁵An alternative dosing regimen would be provision of BID dosing until first morning cortisol is $>100 \text{ nmol/L}$ and then once daily morning dosing until normalization of the HPA axis in asymptomatic children.

⁶While the authors of the statement advocate for the use of daily physiological GC therapy in children with asymptomatic AS and abnormal first morning cortisol to prevent the risk of adrenal crisis, there is no clear evidence to support this. See algorithm 1- 3 which include possible alternative approaches.

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

^aHPA suppression potencies should be used when calculating hydrocortisone equivalent doses for evaluation of AS risk

^bAvailable 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 ⁶⁶⁻⁶⁸

Table 6 – Indications to consider Endocrinology consultation

Table 6 –Indications to *consider* Endocrinology consultation

- Signs or symptoms of AS
- Symptoms of glucocorticoid withdrawal
- First morning cortisol <100 nmol/L
- Abnormal LDST 6-12 months post GC discontinuation
- If LDST indicated and unable to perform without endocrine consult
- Cases where IM teaching is required (i.e. patient has poor access to emergency department or plans remote travel)
- Uncertainty about whether the recommended cortisol thresholds are appropriate for your local laboratory or difficulty interpreting cortisol results (i.e. borderline values)
- Proven or possible AS and receiving CYP3A4 inducers
- Children with “possible AS” who are requiring frequent stress dosing
- Children < 2 years of age with likely, possible or confirmed AS
- Questions or concerns about screening or testing result and the appropriate next steps for management

Algorithm 1: Screening and management of *asymptomatic* children receiving THRESHOLD^A doses of ICS

CURRENT ICS ≥ THRESHOLD

- Educate family about the risk of AS
- Regular re-evaluation of need for high dose ICS
- Regular re-evaluation for symptoms of AS^{1,2}

First morning cortisol value³

<100nmol/L

LIKELY AS

- Initiate/continue stress dosing⁴
- Consider initiation physiologic GCs⁵
- Consult Endocrinology

100-275nmol/L

POSSIBLE AS

- Initiate/continue stress dosing⁴
- Repeat a.m. cortisol³ every 3-6 months
- Follow algorithm below once ICS reduced below threshold dose^A

>275nmol/L

UNLIKELY TO HAVE CLINICALLY SIGNIFICANT AS

- Empiric stress dosing for severe injury or surgery⁴
- Follow algorithm below once ICS reduced below threshold dose^A

ICS REDUCED TO ≤ THRESHOLD

First morning cortisol value³

Initial or repeat a.m. cortisol <150nmol/L

A- LIKELY AS

- Continue stress dosing
- Consider LDST to confirm AS^{6,7}
- Consider continuation/initiation physiologic GCs⁴
- Repeat am cortisol³ every 1-3 months for 6 months or until am cortisol >150 nmol/L
 - Repeat cortisol 150-275nmol/L → Follow pathway B (Possible AS)
 - Repeat cortisol >275nmol/L → Follow pathway C (Unlikely clinically significant AS)
 - Repeat cortisol remains <150 at 6 months → LDST³
- Consult endocrinology if: a) morning cortisol <100nmol/L, b) abnormal LDST at 6-12 months, c) do not have access to ACTH stimulation testing⁷

Initial am cortisol 150-275nmol/L

B- POSSIBLE AS

- d/c daily GC therapy
- Continue stress dosing
- Perform LDST or empiric stress dosing⁷
 - Normal LDST: d/c stress dosing and d/c follow-up
 - Abnormal LDST: repeat at 6-12 months.
- 5) Referral to endocrinology if LDST abnormal at 6-12 months

Initial am cortisol >275nmol/L

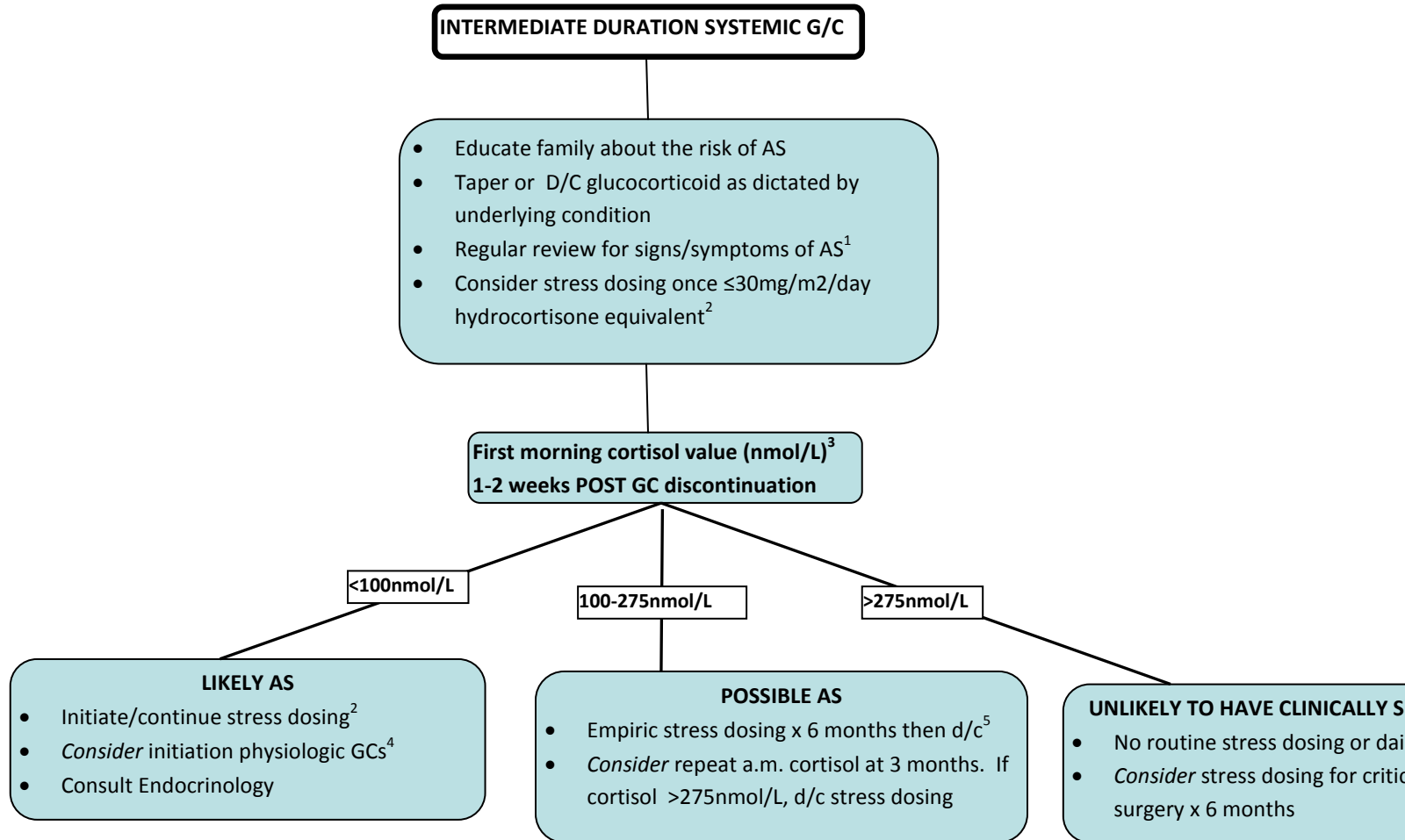
C – UNLIKELY TO HAVE CLINICALLY SIGNIFICANT AS

- d/c daily and stress dosing for moderate illness or surgery
- Consider stress dosing for severe illness or surgery
- Consider LDST to confirm AS⁸

Algorithm 1 – footnotes, management options and controversies

- ^A See Table 2 – Threshold doses ICS
- ¹ See Table 1 – Symptoms/Signs of possible AS
- ² Follow Algorithm 4 if symptomatic
- ³ See table 3 for testing procedures
- ⁴ See table 4 for glucocorticoid dosing, see Appendix 2 for stress dosing card
- ⁵ While the authors of the statement advocate for the use of daily physiological GC therapy in children with asymptomatic AS and abnormal first morning cortisol to prevent the risk of adrenal crisis, there is no clear evidence to support this. Some endocrinologists do not treat with physiological GC in asymptomatic children.
- ⁶ Consideration of a LDST should be made prior to ongoing daily GC therapy, especially in children at lower risk of AS (i.e. shorter duration of GC therapy) or children with abnormal sleep wake cycles (i.e. children <2 years of age), secondary to the poor specificity of a first morning cortisol.
- ⁷ If uncertain about availability of LDST, consult your local endocrinologist. In some cases, empiric stress dosing x 1 year may be a reasonable alternative to dynamic testing.
- ⁸ A screening threshold of >275nmol/L is often used in clinical practice to rule out AS while an am cortisol >350-500nmol/L is needed to definitively rule out AS. Therefore in children at greater risk, empiric GC therapy for 1 year or a LDST to definitively rule out AS might be considered.

Algorithm 2: Screening and management of *asymptomatic* children POST DISCONTINUATION of intermediate duration (2-4 weeks) systemic GC therapy



Algorithm 2 - management options and controversies

- ¹Follow algorithm 3 if symptomatic
- ²See table 4 for stress dosing, Appendix 2 for stress dosing cards
- ³See table 3 for testing procedures
- ⁴While the authors of the statement advocate for the use of daily physiological GC therapy in children with asymptomatic AS and abnormal first morning cortisol to prevent the risk of adrenal crisis, there is no clear evidence to support this. *See table 4 for physiological dosing.*
- ⁵If frequent stress dosing required or anticipated, perform LDST and refer to endocrinology if abnormal.

Algorithm 3: Screening and management of *asymptomatic* children AFTER DISCONTINUATION of long duration (>4 weeks) systemic GC therapy

>4 WEEKS SYSTEMIC GC THERAPY

- Empiric stress dosing for illness, injury or surgery until evaluation of the HPA axis¹
- Educate family about the risk of AS
- Regular review for signs/symptoms of AS post taper or discontinuation of GC^{2,3}

Gradual taper dictated by the underlying condition
First morning cortisol⁴ 1-2 weeks after reducing GCs to physiologic dose⁵

Systemic GC and no taper indicated for management of the underlying condition
Rapid GC taper to physiologic dose⁵ and perform first morning cortisol⁴ 1-2 weeks later

First morning cortisol value

Initial or repeat a.m. cortisol

A-LIKELY AS

- Continue stress dosing
- Consider LDST to confirm AS⁴
- Consider continuation/initiation physiologic GCs^{1,6}
- Repeat am cortisol⁴ every 1-3 months for 6 months or until am cortisol >150 nmol/L
 - Repeat cortisol 150-275nmol/L → Follow pathway B (Possible AS)
 - Repeat cortisol >275nmol/L → Follow pathway C (Unlikely clinically significant AS)
 - Repeat cortisol remains <150 at 6 months → LDST⁷
- Consult endocrinology if: a) morning cortisol <100nmol/L, b) abnormal LDST at 6-12 months, c) do not have access to ACTH stimulation testing⁸

Initial am cortisol 150-275nmol/L

B – POSSIBLE AS

- d/c daily GC therapy
- Continue stress dosing
- Perform LDST or empiric stress dosing⁸
 - Normal LDST: d/c stress dosing and d/c follow-up
 - Abnormal LDST: repeat at 6-12 months.
- 5) Referral to endocrinology if LDST abnormal at 6-12 months

Initial am cortisol >275nmol/L

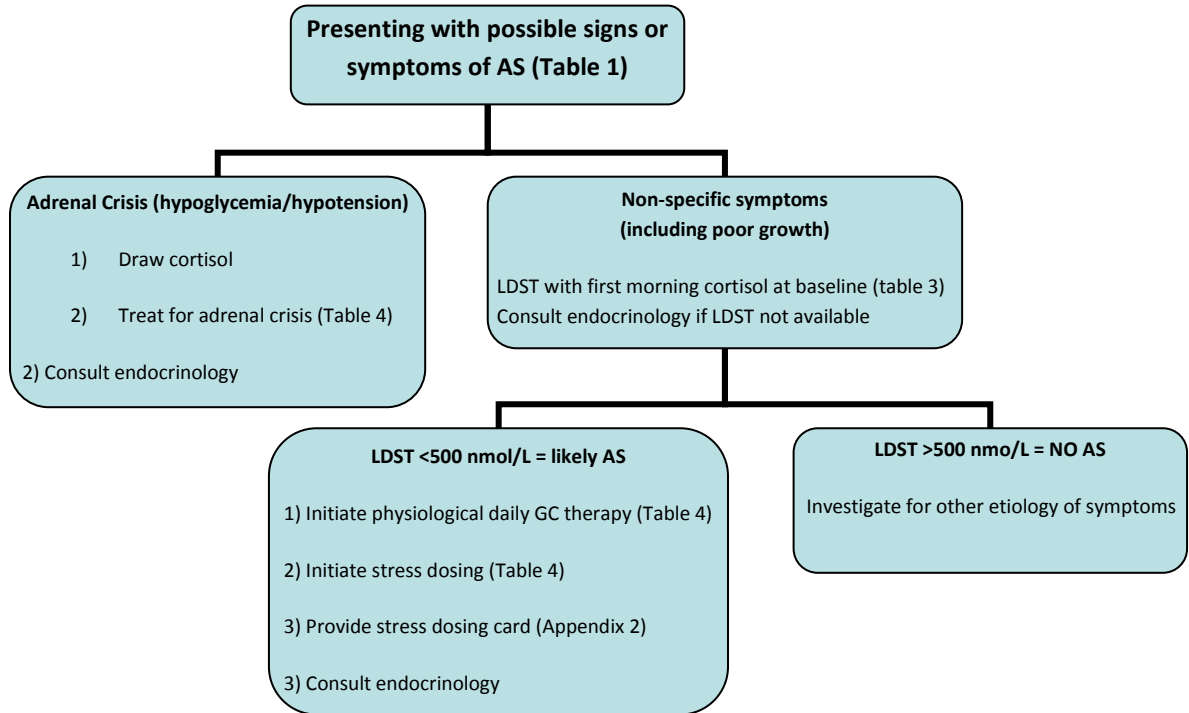
C – UNLIKELY CLINICALLY SIGNIFICANT AS

- d/c daily and stress dosing for moderate illness
- Consider stress dosing for critical illness or surgery for 1 year⁹
- Consider LDST to definitively r/o AS⁹

Algorithm 3 – footnotes, management options and controversies

- ¹ See table 4 for glucocorticoid therapy including stress dosing, see Appendix 2 for stress dosing cards
- ² See Table 1 – Symptoms/Signs of possible AS
- ³ Follow Algorithm 4 if symptomatic
- ⁴ See table 3 for testing procedures
- ⁵ Physiological hydrocortisone dose = 8mg/m²/day. See table 5 for glucocorticoid equivalencies.
- ⁶ While the authors of the statement advocate for the use of daily physiological GC therapy in children with asymptomatic AS and abnormal first morning cortisol to prevent the risk of adrenal crisis, there is no clear evidence to support this. Some endocrinologists do not treat with physiological GC in asymptomatic children.
- ⁷ Consideration of a LDST should be made prior to ongoing daily GC therapy, especially in children at lower risk of AS (i.e. shorter duration of GC therapy) or children with abnormal sleep wake cycles (i.e. children <2 years of age), secondary to the poor specificity of a first morning cortisol.
- ⁸ If uncertain about availability of LDST, consult your local endocrinologist. In some cases, empiric stress dosing x 1 year may be a reasonable alternative to dynamic testing.
- ⁹ A screening threshold of >275nmol/L is often used in clinical practice to rule out AS while an am cortisol >350-500nmol/L is needed to definitively rule out AS. Therefore in children at greater risk, empiric GC therapy for 1 year or a LDST to definitively rule out AS might be considered.

Algorithm 4: Testing procedure for *symptomatic* children on GC with possible AS



Appendix 2: Sample Wallet Cards

Example 1 – Sample Wallet Card (hydrocortisone).

SAMPLE WALLET CARD – PROVEN OR POSSIBLE AS
_____ has/is at risk of adrenal suppression secondary to GC use for _____ They require hydrocortisone for: ☐ Daily replacement and stress dosing ☐ Stress dosing only ☐ Stress dosing for severe illness/severe injury or surgery only Daily hydrocortisone dose (if applicable): _____ BSA: _____m² Date: _____ All children with confirmed or suspected adrenal suppression must receive extra glucocorticoids in times of physiologic stress. See reverse for stress dosing guidelines.

STRESS DOSING	
PARENTS AND PHYSICIANS	
Moderate illness including Fever >38.5, severe head cold, vomiting, injury, lethargy	30 mg/m ² /day hydrocortisone equivalent, divided TID This dose is equal to _____mg of hydrocortisone 3 times daily
PARENTS	
Severe illness or injury or unwell and unable to tolerate oral medications	If you have injectable hydrocortisone at home, give ____mg (____ml) immediately Go to emergency department Consider calling EMS if severe illness or injury
PHYSICIANS	
Severe illness, Adrenal crisis or severe injury	Hydrocortisone 100 mg/m ² (max 100mg) IV/IM Call Endocrinologist on call
Unable to tolerate orally	Hydrocortisone 25 mg/m ² /dose q6 h IV or q 8h IM (if requiring ongoing parenteral administration after 24 hours, consult endocrinology)
Surgery	Hydrocortisone 50-100 mg/m ² IV with induction (max 100 mg). Call Endocrinologist on call.

Appendix 2 (continued)

Example 2 – Sample Wallet Card (Prednisone on active therapy)

SAMPLE WALLET CARD – ON ACTIVE THERAPY	
_____ is currently receiving Prednisone therapy for _____ He/she is at risk of adrenal suppression related to glucocorticoid therapy BSA: _____m² Date: _____ All children with confirmed or suspected adrenal suppression must receive extra glucocorticoids in times of physiologic stress. See reverse for stress dosing guidelines.	

STRESS DOSING	
PARENTS AND PHYSICIANS	
Moderate illness including Fever >38.5, severe head cold, vomiting, injury, lethargy	1) If your child is still above a prednisone dose of ____mg (7.5mg/m ² /day) divide this dose into two doses one given in the morning and one in the evening. 2) If child is below this dose, increase prednisone to ____mg (7.5mg/m ² /day) given twice a day.
PARENTS	
Severe illness or injury or unwell and unable to tolerate oral medications	If you have injectable hydrocortisone at home, give ____mg (____ml) immediately Go to emergency department Consider calling EMS if severe illness or injury
PHYSICIANS	
Severe illness, Adrenal crisis or severe injury	Hydrocortisone 100mg/m ² (max 100mg) IV/IM Call Endocrinologist on call.
Unable to tolerate orally	Hydrocortisone 25mg/m ² /dose q6 h IV or 8h IM (if requiring ongoing parenteral administration after 24 hours, consult endocrinology)
Surgery	Hydrocortisone 50-100mg/m ² IV with induction (max 100 mg). Call Endocrinologist on call.

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