

Adrenal suppression from glucocorticoids: preventing an iatrogenic cause of morbidity and mortality in children

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To cite: Ahmet A, Mokashi A, Goldbloom EB, *et al*. Adrenal suppression from glucocorticoids: preventing an iatrogenic cause of morbidity and mortality in children. *BMJ Paediatrics Open* 2019;**3**:e000569. doi:10.1136/bmjpo-2019-000569

Received 19 August 2019
Revised 26 September 2019
Accepted 28 September 2019

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, healthcare 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 healthcare professionals.

INTRODUCTION

Glucocorticoids (GCs), including inhaled corticosteroids (ICS), are essential for the treatment of many paediatric 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 corticotropin-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 the release of ACTH at the level of the pituitary gland, in turn, downregulating cortisol production and secretion. Exogenous GCs 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 GC exposure is also referred to as adrenal suppression (AS).^{3–5}

AS is the most common form of AI among 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 (box 1) and can go undetected until a physiological stress (illness, surgery, injury) precipitates an adrenal crisis.⁶ Adrenal crisis has also been reported in the absence of physiological stress, likely secondary to unrecognised signs or symptoms of AS.^{2,6} Symptomatic AS including adrenal crisis can be prevented by recognising children at risk and administering physiological 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 paediatric population, evidence-based guidelines about screening



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Box 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
- ▶ Hypoglycaemia (seizure/coma)

Signs associated with adrenal suppression

- ▶ Cushingoid features

*Poor linear growth has been reported in close to 50% of patients with symptomatic adrenal suppression.⁸ Adapted from Ahmet et al.⁴

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 among paediatric 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 paediatric endocrinologists, paediatricians and other paediatric 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.

AS in children treated with systemic GCs

Both clinical and biochemical evidence of AS have been well described in children after 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 after 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.^{5 18 19}

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

AS in children treated for asthma with ICS

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 the criteria for treatment with high (or moderate) dose ICS therapy.^{20–22}

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 1](#)). 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 interindividual variation in GC sensitivity⁵ 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 interpatient 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 puts 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 body mass index and cumulative GC exposure.^{2 8} Duration of ICS exposure has

Table 1 ICS type and doses associated with increased adrenal suppression risk*

Corticosteroid	Dose associated with increased AS risk † (µg/day) Canadian/European dosing	Dose associated with increased AS risk † (µg/day) American dosing
Beclomethasone dipropionate HFA ²⁶	>400	>320
Budesonide DPI ^{8 26} Budesonide and formoterol	≥800	≥800
Ciclesonide‡	>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

*Doses associated with increased risk of AS are based on the best available literature. Where no specific evidence for AS risk in paediatrics 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 recognising that AS is possible even with low to moderate dosing.

†In the USA, 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.

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

§Fluticasone furoate (Arnuity Ellipta and Breo Ellipta) contains a new potent ICS. 100 µg daily is equivalent to 500 µg daily of fluticasone. This formulation has a high potential risk for AS.²⁷

AS, adrenal suppression; DPI, dry-powder inhaler; HFA, hydrofluoroalkane; ICS, inhaled corticosteroids.

not been found to be a risk factor; however, most studies have looked at exposures of 6 weeks or more.^{3 5 11 34}

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 1).

AS in children treated with other forms of GCs

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.^{36–38}

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 GCs

CYP3A4 inhibitors, including several antiretroviral medications, antifungal agents and select antidepressants, prolong the biologic half-life of GCs. These medications have been reported (1) in several cases of symptomatic AS associated with relatively low doses of ICS, and (2) with a prolonged duration of AS after systemic GC exposure.^{10 45 46}

GC 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 (<8 mg/m²/day hydrocortisone equivalent) should be considered in children who have received prolonged courses of GCs (table 2, 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.

Table 2 Relative glucocorticoid potencies*

	Anti-inflammatory potency	HPA suppression potency†	Duration of action (h)
Hydrocortisone (cortisol)	1	1	8–12
Prednisone	4	4	12–36
Prednisolone	4	4	12–36
Methylprednisolone	5	5	12–36
Dexamethasone	30	50 (17–100)	36–72

*HPA suppression potencies should be used when calculating hydrocortisone equivalent doses for evaluation of AS risk.

†Available data about relative HPA suppression potency are 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.^{71–73}

AS, adrenal suppression; HPA, hypothalamic–pituitary–adrenal.

Testing for AS

Testing for AI, including AS, is a challenge for clinicians due to lack of standardisation 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 (07:00–09:00) is often used in screening for AI. A first morning cortisol is specific for diagnosis of AI if ≤ 100 nmol/L (≤ 3.6 $\mu\text{g}/\text{dL}$) 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 – 500 nmol/L (≥ 13 – 18 $\mu\text{g}/\text{dL}$) can predict normal HPA axis function.^{53 55 56} The Paediatric Endocrine Society Pharmacy and Therapeutics guideline about endocrine side effects of ICS suggests that a first morning cortisol value of 275 nmol/L (10 $\mu\text{g}/\text{dL}$) may be considered as a screening threshold in asymptomatic patients.² However, there is no single absolute cut-off 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 (250 μg) and low dose (1 μg) 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 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 (16–22 $\mu\text{g}/\text{dL}$) are commonly used to rule out AI but varies between studies and institutions since many factors must be considered when interpreting results (eg, 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](#)).

GC 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

Table 3 Tests of HPA axis function: considerations for testing

Procedure	Considerations for testing
All tests	<ul style="list-style-type: none"> ▶ Hold all oral GCs prior to the test based on their duration of action*: <ul style="list-style-type: none"> – hydrocortisone \times 24 hours, – prednisone \times 48 hours, – dexamethasone \times 72 hours ▶ Consideration of a switch to hydrocortisone prior to testing should be considered in children at high risk of AS* ▶ Hold ICS the evening and morning prior to the test if patient stable†
First morning cortisol ‡	<ul style="list-style-type: none"> ▶ 07:00–09:00 test (before 08:00 is optimal) ▶ Tests drawn after 09:00 must be repeated if abnormal
Low dose ACTH stimulation§	<ul style="list-style-type: none"> ▶ Perform test in the morning⁷⁴ ▶ 1 μg corticotropin analogue^{5¶} ▶ Minimal tubing length for administration of corticotropin reduces the possibility of adherence to plastic tubing⁷⁴ ▶ Cortisol drawn at 0, 15, 30 and 60 min for peak levels⁵⁸
Standard dose ACTH stimulation	<ul style="list-style-type: none"> ▶ 250 μg§ corticotropin analogue ▶ Cortisol drawn at 0, 30 and 60 min ▶ Currently no evidence to support morning vs afternoon testing

*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.

†In children where it is unsafe to hold evening inhaled corticosteroid dose, abnormal cortisol levels must be interpreted with caution.

‡In infants and children with disrupted sleep–wake cycles, an abnormal first morning cortisol is not diagnostic of AS. Provocative testing is indicated.

§For infants: corticotropin dose=15 $\mu\text{g}/\text{kg}$ up to a maximum dose of 250 μg .

¶Careful dilution and timely administration of corticotropin is required.⁷⁴

**Protocols for low-dose ACTH stimulation tests including timing of cortisol samples may vary between institutions.

††Provocative testing is required to definitively rule in or out AS. ACTH, adrenocorticotropic hormone; AS, adrenal suppression.

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 are 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

Table 4 Glucocorticoid replacement and stress dosing

Indication	Glucocorticoid dose*†
Adrenal crisis, severe illness or severe injury	Hydrocortisone 100 mg/m ² (max 100 mg) intravenous/intramuscular stat, then 100 mg/m ² (max 200 mg) divided every 6 hours or by continuous infusion
Major surgery	Hydrocortisone 50–100 mg/m ² intravenous (max 100 mg) pre-op, then 100 mg/m ² /24 hours intravenous (max 200 mg) by continuous infusion or divided every 6 hours
Minor to moderate surgery or procedure requiring general anaesthesia	Hydrocortisone 50 mg/m ² intravenous (max 100 mg) pre-op, then as indicated by clinical status (typically moderate illness dosing × 1–2 days)
Moderate illness including fever ≥38.5°C, vomiting, diarrhoea, severe head cold with fatigue or injury <i>Able to tolerate orally</i>	30 mg/m ² /day hydrocortisone equivalent‡ divided three times a day until resolution of symptoms Duration >3 days should be reassessed by the healthcare team§
Moderate illness including fever ≥38.5°C, vomiting, diarrhoea, severe head cold with fatigue or injury <i>Inability to tolerate orally</i>	Hydrocortisone must be given parenterally 30–50 mg/m ² /day hydrocortisone divided every six hourly intravenous or every eight hourly intramuscular 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 intramuscular 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, and so on) should be taught administration of intramuscular hydrocortisone

Daily physiological hydrocortisone dosing

 8 mg/m²/day hydrocortisone daily (divided two to three times per day if symptomatic with higher dose in the morning)

*Poor evidence for paediatric dosing. Recommendations based on expert opinion and best available evidence.^{6 66–68}

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

‡In children on active therapy in doses ≥30 mg/m²/day hydrocortisone equivalent (≥7.5 mg/m²/day prednisone), stress dosing for mild-moderate illness can be achieved by dividing the therapeutic prednisone dose to be given two times per day (ie, therapeutic dose is sufficient for stress coverage). Once therapeutic glucocorticoid is no longer needed, stress dosing should be provided using hydrocortisone.

§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.

AS, adrenal suppression; ED, emergency department.

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 2 for relative potencies).

Children with symptomatic AS require daily physiological GC replacement (table 4).² 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 paediatric 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 8 mg/m²/day considered to be physiological.^{65 66} While three times per day 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 reduce the risk of prolonging suppression. Clinicians must be aware of the short half-life of hydrocortisone and provide two or three times per day dosing if a child is symptomatic and three times per day 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 minimise 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/m²/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 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 paediatric conditions and that the risk of AS should not be a barrier to their use.

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Acknowledgements We would like to thank Victor Konji (PhD) for his assistance with our literature review and article referencing.

Contributors 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, finalised edits submitted by authors and contributed her expertise as a paediatric endocrinologist. AM, EBG, CH and PK (paediatric endocrinologists) participated in teleconferences informing the content of the review article, reviewed and edited the manuscript, and contributed their expertise as paediatric endocrinologists. TK (paediatric respirologist), RJ (paediatric rheumatologist) and HK (allergist) participated in teleconferences informing the content of the review article, reviewed and edited the manuscript, and contributed their expertise as subspecialists who frequently prescribe glucocorticoids (GCs). 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 paediatricians who prescribe GCs to the recommendations. All authors approved the final revised manuscript as submitted and agree to be accountable for all aspects of the work.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests AA has received honoraria as a consultant to Reveragen. HK has served as a speaker and/or advisor for ALK, Aralez, Astrazeneca, CSL Behring, Shire, Novartis, PediaPharm, Stallergenes, Kaleo, Sanofi, Pfizer and Mylan.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement There are no data in this work.

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