CLINICAL PRACTICE

Asthma treatment in children: A guide to screening for and management of hypothalamic-pituitary-adrenal axis suppression

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A recently published approach to paediatric asthma management neither recommended screening for nor suggested any management of hypothalamic-pituitary-adrenal axis suppression in asthmatic children treated with corticosteroids. The existing literature on this topic was therefore reviewed and the quality of the evidence assessed. Recommendations for diagnosis, screening and management are made utilising the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

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Inhaled corticosteroids (ICS) and to a lesser extent nasal steroids (NS) have undoubtedly revolutionised asthma therapy and improved quality of life in a cost-effective way. However, current evidence suggests that every asthmatic child on corticosteroids is at risk of hypothalamic-pituitary-adrenal axis suppression (HPAS). As most patients with this complication are asymptomatic, those most at risk should be screened. If screening is inconclusive, adrenal function testing should be performed. On the basis of its outcome the most appropriate management should be determined.

In a recently published approach to paediatric asthma management,[1] treatment modifications included a 3-day course of rescue oral corticosteroids, intermittent use of ICS, a single ICS dose in the morning if possible, and a more prominent role for non-steroid controller medication. All these measures will protect the hypothalamic-pituitary-adrenal axis from suppression. However, the article neither recommended screening for nor suggested any management of HPAS.

Whenever exogenous corticosteroids are prescribed, endogenous cortisol production is reduced. This 'systemic effect' is determined by the dose, delivery device, technique, adherence, body surface area, body mass index (BMI) and duration of therapy, the number of corticosteroids being used and their pharmacokinetic characteristics, and genetic and epigenetic factors.[2-4] Age and gender are not predictors, unless the dose has not been adjusted to body surface area.[5] At supraphysiological ICS doses, 50% of children can be expected to develop HPAS,[2] while at physiological doses (i.e. a cortisol production rate of 3.0 - 10.6 mg/m^2)[6] dose and effect have an inverse relationship.[2] Hypocortisolaemia has even been described at physiological doses.[2,7,8] HPAS is usually seen in all children after 6 - 42 months of ICS therapy,[3] but has been observed as early as 2 months (EWZ, unpublished data, 2011). Under basal conditions no untoward effects will be apparent, because the decreased production of cortisol is balanced by the supply of exogenous corticosteroids. In the long term, the adrenal glands may atrophy. During a stressful event such as an infection, injury, burn or surgical operation, or even an asthma exacerbation, demand for cortisol may outstrip its exogenous supply. The stress can precipitate an adrenal crisis, which may lead to death. When CYP3A4 enzyme inhibitors (antiretrovirals, antifungals, calcium-channel blockers, certain antibiotics and antidepressants)[9] are coadministered, metabolism of corticosteroids is reduced, resulting in HPAS or Cushing's syndrome.[10]

In order to make recommendations for diagnosis, screening and management of HPAS in asthmatic children, I have reviewed the existing literature and presented the quality of the evidence assessed in three tables. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used. It classifies the quality of the evidence as high, moderate, low or very low, with the recommendations being either strong or weak.[11] Management suggestions that could not be substantiated by evidence are labelled 'ungraded best practice'.[12]

Diagnosis of HPAS

HPAS presents as a spectrum (Table 1). Adrenal crisis is the most devastating presentation, but occurs rarely.[13] Chronic adrenal insufficiency (CAI) is frequently overlooked owing to its nonspecific clinical features.[7] For these reasons it is essential to diagnose HPAS in its subclinical state. The overnight metyrapone test should be used to make the definitive diagnosis of HPAS.[14] If metyrapone is not available, the 0.5 µg/1.73 m^2 adrenocorticotrophic hormone (ACTH) stimulation test is a good second choice, provided serum cortisol levels are measured at 10, 15, 20, 25, 30 and 35 minutes.[15] Clinicians utilising the ACTH stimulation test need to be aware of several pitfalls.[16] Interpretation of results is assay specific. In 2015, Roche launched its Elecsys Cortisol II assay. It is more specific than the older cortisol assay and shows lower cross-reactivity, generating cortisol levels that are ~30% lower.[17] The pass criterion for the test therefore has to be down-adjusted to 350 nmol/L (from 500 nmol/L). No adjustments need to be made for levels <250 nmol/L, because the old and new assays correlate well at lower levels.

Screening for HPAS

Screening for HPAS (Table 2) is problematic, because no useful screening test has been identified so far.[18] Measurement of early-

Table 1. Diagnostic features of HPAS

Presentation	Clinical features	Serum cortisol	Strength of recommendation/level of evidence
Clinical			
Adrenal crisis	Hypoglycaemia* – depressed level of consciousness/coma, convulsions; nausea (hypotension, syncope, severe weakness, abdominal pain, vomiting, backache, hyponatraemia, hyperkalaemia, hypercalcaemia)†	Usually <138 nmol/L	Strong/moderate
CAI	Lassitude, weakness, dizziness, nausea, headache, poor growth, weight loss, (orthostatic hypotension)†	<138 nmol/L at 08h00 - 10h00	Weak/very low
Subclinical			
Hypocortisolaemia	Inability to respond appropriately to stress	<138 nmol/L at 08h00 - 10h00	Weak/low
Failed adrenal function test‡	Inability to respond appropriately to stress	138 - 350 nmol/L§ at 08h00 - 10h00	Strong/moderate

HPAS = hypothalamic-pituitary-adrenal axis suppression; CAI = chronic adrenal insufficiency; ACTH = adrenocorticotrophic hormone.
*Hypoglycaemia is the most common presentation of adrenal crisis in the paediatric age group.
†These clinical/laboratory findings are classic features, but have not been described in case series.
‡Metyrapone or 0.5 μg/1.73 m² ACTH stimulation test.
§As measured by the Elecsys Cortisol II assay.

Table 2. Screening recommendations for subclinical HPAS

		Strength of recommendation/level of evidence
Patients at highest risk	A. On a supraphysiological total steroid dose (ICS + NS), i.e. >10.6 mg HC equivalent/m²/d (>BUD 848 μg/m²/d or >FP 424 μg/m²/d given by MDI + spacer)	Strong/moderate
	B. On a physiological total steroid dose (≤10.6 mg HC equivalent/m²/d)	
	On multiple steroids	
	ICS + prednisone: daily, alternate-day or recurrent 5-day courses <10 days apart	Strong/low
	ICS + NS	Strong/moderate
	ICS + topical potent steroids*	Strong/low
	Adherent to ICS + NS therapy	Strong/high
	BMI *z*-score <0†	Strong/moderate
	On an enzyme inhibitor	Strong/varies with inhibitor
Screening test interpretation	Serum cortisol at 08h00 - 10h00	
	<138 nmol/L: hypocortisolaemia	Weak/low
	>350 nmol/L‡: normal axis	Weak/low
	138 - 350 nmol/L: refer for metyrapone or 0.5 μg/1.73 m² ACTH stimulation test	Strong/moderate
Screening frequency	If serum cortisol > 350 nmol/L, screen 6-monthly if steroid dose not reduced	Ungraded best practice

HPAS = hypothalamic-pituitary-adrenal axis suppression; ICS = inhaled corticosteroids; NS = nasal steroids; HC = hydrocortisone; BUD = budesonide; FP = fluticasone propionate; MDI = metered-dose inhaler; BMI = body mass index; ACTH = adrenocorticotrophic hormone.
*Clobetasol propionate, betamethasone valerate, hydrocortisone butyrate.
†BMI *z*-score 0 - 2 does not exclude HPAS, but <0 is more likely.
‡As measured by the Elecsys Cortisol II assay.

morning salivary cortisone has been suggested,[19] but its routine use is premature because it has not been evaluated against a gold-standard adrenal function test. Its low positive predictive value would also argue against its use. Endocrinologists diagnose adrenal insufficiency when the 08h00 - 10h00 serum cortisol level is <138 mmol/L,[12,20,21] while a serum cortisol level of >350 nmol/L (as measured with the Elecsys Cortisol II assay) virtually excludes HPAS.[21] A 06h00 - 08h00 serum cortisol level of <83 nmol/L to suggest HPAS would be ideal,[2] but may be impractical. There is no scientific basis for labelling a level >276 nmol/L as safe.[22] Given the poor performance of the serum cortisol screen, only patients at high risk should be screened. If the results are inconclusive, the patient should be referred to an endocrinologist for definitive testing.

In order to identify patients at high risk, meticulous attention should be paid to an individual asthma patient's treatment, the corresponding doses and calculation of the total steroid dose, relating this to body surface area. In addition, cognisance needs to be taken of the child's BMI, adherence to therapy and the ICS route of administration, as lung deposition, and hence dose, varies between devices.[1,3]

Table 3. Management recommendations for HPAS

	Management	Strength of recommendation/ level of evidence
Clinical HPAS		
Adrenal crisis	HC 2 mg/kg (50 - 100 mg/m^2) IV bolus, followed by HC 2 mg/kg/d (50 - 100 mg/m^2/d) IV divided 6-hourly	Strong/moderate
	For hypoglycaemia: 5 mL/kg of 10% DW IV at 3 mL/kg/h	Ungraded best practice
	If in shock, treat with normal saline (0.9%) 20 mL/kg (maximum 60 mL/kg within 1 hour)	Ungraded best practice
CAI	HC orally at 8 mg/m^2/d, ⅔ given in the morning, ⅓ 2 hours after lunch; continued for about 1 year until axis has recovered	Weak/low
	Modify asthma therapy by reducing steroid load on the axis	Weak/low
	Substitute lower ICS and NS dose by using steroid-sparing medication	
	If possible, prescribe single morning dose of ICS and NS	
	If possible, use newer-generation NS*	
	Aim for a steroid load of HC ≤6 mg/m^2/d (BUD 480 µg/m^2/d or FP 240 µg/m^2/d given by MDI + spacer)	
Subclinical HPAS		
Hypocortisolaemia	As for CAI	Ungraded best practice
Failed adrenal function test	As for CAI, but omit HC	Ungraded best practice
Sick-day management		
Home management of illness with fever		Ungraded best practice
>38°C	Double HC replacement until recovery (usually 3 days)	
>39°C	Treble HC replacement until recovery (usually 3 days)	
Unable to tolerate oral therapy due to gastroenteritis or trauma	HC IM/SC given at a bolus dose of 50 mg for primary school age children and 100 mg for adolescents; continue IV/IM as for adrenal crisis or switch to oral regimen depending on clinical state	Ungraded best practice
Asthma exacerbation	If prednisone is given, there is no need to give HC as well	Ungraded best practice
Minor surgery	Double or treble HC dose	Ungraded best practice
Major surgery, trauma or disease requiring intensive care	IV HC regimen as for adrenal crisis, but tapering rapidly and switching to oral regimen depending on clinical state	Ungraded best practice
Additional management	Medic Alert bracelet	Ungraded best practice
	Educate family	Ungraded best practice

HPAS = hypothalamic-pituitary-adrenal axis suppression; HC = hydrocortisone; IV = intravenous; DW = dextrose water; CAI = chronic adrenal insufficiency; ICS = inhaled corticosteroids; NS = nasal steroids; BUD = budesonide; FP = fluticasone propionate; MDI = metered-dose inhaler; IM = intramuscular; SC = subcutaneous.
*Fluticasone, ciclesonide, mometasone.

Management of HPAS

Management of adrenal crisis is life-saving (Table 3). Treatment modification (besides hydrocortisone) for CAI or subclinical HPAS is essentially the same. The aim of the intervention is to keep the total steroid dose well within the lower-normal physiological range.[2] Steroid-sparing controllers available include leukotriene receptor antagonists, long-acting beta-agonists, long-acting theophylline, tiotropium bromide, and the biological agents omalizumab, mepolizumab and dupilumab.[1,23] Early-morning dosing of inhaled and nasal budesonide, ciclesonide, mometasone, and fluticasone propionate and furoate should be prescribed whenever symptom control allows it, thereby ensuring that the early-morning surge of ACTH is not suppressed. These four drugs have minimal systemic absorption.[24] Should HPAS develop while on nasal beclomethasone or budesonide, nasal therapy should therefore be switched to one of the newer agents. However, beclomethasone is the preferred ICS/NS for any child treated with an enzyme inhibitor in addition to a steroid, because it is not metabolised by cytochrome P450.[10] Rescue oral corticosteroids should never be given for more than 3 days[25] and should not be provided to parents to be used when necessary.

Treatment modification for HPAS has been found to be effective.[26] Even when ICS doses are not reduced, HPAS seems to resolve in some patients.[27] This may be due to poor adherence to therapy or an increase in airway diameter with age, resulting in better control with reduced ICS doses.

Conclusions

Any asthmatic child on corticosteroids may develop HPAS. In the absence of clinical features, serum cortisol should be used to screen those most at risk. Screening should start 6 months into therapy and include children on supraphysiological steroid doses, those on multiple steroids or enzyme inhibitors, and those adherent to therapy or who are thin. If screening is inconclusive, adrenal function testing should be performed by a paediatric endocrinologist. Appropriate management, including asthma therapy modification, should be instituted if necessary.

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