

CASE REPORT

Adrenal Suppression and Exogenous Cushing Syndrome After Inhaled and Topical Corticosteroids – Two Clinical Cases and Review of the Subject

Gheorghe Serpoi¹, Constantin Cucu^{2,3}

Abstract

The undesirable endocrine effects associated with pharmacological therapy with corticosteroids administered orally or parenterally are well-known in medical practice. However, the degree of vigilance is lower when compartmental corticosteroids are used, and it is a widely held assumption that local glucocorticoids rarely produce adrenal insufficiency or exogenous Cushing syndrome. The two cases that we present here demonstrate the appearance of major adrenal suppression and Cushing exogenous syndrome after inadequate use of topical corticosteroids and, the combination of inhaled corticosteroids with nasal glucocorticoids, respectively. The following mini-review shows, from the endocrinologist point of view, the main aspects to be considered by practitioners who recommend local glucocorticoid treatments – i.e. inhaled, topical (cutaneous, oral, nasal, ophthalmic) or intraarticular – to prevent the occurrence of major endocrine syndromes that are met after corticosteroid therapy, tertiary adrenal insufficiency and exogenous Cushing syndrome.

Keywords: corticosteroid administration; adrenal suppression; exogenous Cushing

Rezumat

Efectele endocrine nedorite asociate terapiei farmacologice cu corticosteroizi administrați oral sau parenteral sunt bine cunoscute în practica medicală. Gradul de vigilență este, însă, mai redus atunci când se folosesc corticosteroizi administrați compartimental, față de care părerea generală este că ar produce arareori insuficiență adrenală sau sindrom Cushing exogen. Cele două cazuri pe care le prezentăm demonstrează apariția de supresie adrenală importantă și de sindrom Cushing exogen după folosirea inadecvată a dermatocorticoizilor și, respectiv, a combinației de corticosteroizi inhalatori cu glucocorticoizi nazali. Mini-sinteza care urmează prezintă, din perspectiva endocrinologului, principalele aspecte care ar trebui să fie avute în vedere de către practicienii care recomandă tratamente cu glucocorticoizi administrați local - inhalator, topic (cutanat, oral, nazal, oftalmic) sau intra-articular - pentru a preveni apariția sindroamelor endocrine majore generate de corticoterapie: insuficiența adrenală terțiară și sindromul Cushing exogen.

Cuvinte-cheie: corticoterapie; supresie adrenală; Cushing exogen

¹ Department of Endocrinology, CF2 Clinical Hospital Bucharest, Romania

² „Carol Davila” University of Medicine and Pharmacy, Bucharest, Romania

³ „C.I. Parhon” National Institute of Endocrinology, Bucharest, Romania

Corresponding author:

Gheorghe Serpoi, Clinical Department of Endocrinology, CF2 Hospital, 63-65 Marasti Avenue, Bucharest, Romania.
E-mail: gserpoi@gmail.com

INTRODUCTION

Corticosteroid (CS) therapy is used by 1% of world population, especially for non-endocrinological indications. Compartmental administration of CS (i.e. topical, inhaled or intraarticular) was developed to prevent undesired effects. Still even these therapies could generate major endocrine syndromes, as our two cases tend to illustrate – Table 1 and Table 2.

Table 1. Case no. 1 description

TC, male, born in 1960, was evaluated in May 2016, referred by rheumatologist after radiological evidences of vertebral crushes. Patient, a trained athlete, with psoriasis from the age of 26 was exposed the last two years to intense local glucocorticoid (GC) therapy – daily applications and weekly occlusive therapy (“wrapping”) with a highly potent topical agent, class I, clobetasol-propionate cream 0.05% using an average of 200-225 g/week, i.e. 14mg clobetasol/day.				
2016, May. Clinical Exam: Height=179 cm; Weight=124Kg; Body-mass index=38.7 Kg/m ² ; heart rate=68/min, regular; blood pressure = 140/95 mmHg; plethoric facies; Cushingoid fat redistribution and muscular wasting at the level of proximal groups; thin skin, with widespread exfoliation and areas of atrophy at abdominal level, antero-axillar striae and on the flanks; facial telangiectasia and ecchymosis of various ages on the arms and forearms; psoriatic lesions on elbows, knees, legs and the anterior wall of the abdomen; varicosities at the lower members, with stasis dermatitis and venous ulcer on the external part of the right leg.				
Hormonal testing (blood, 8AM)	May 2016* 1 st visit	August 2016** 2 nd visit	August 2017** 3 rd visit	Feb 2018** 4 th visit
Cortisol range: 101-535 nmol/L (3.7-19.4 ug/dl)	4.83 nmol/L (0.17 ug/dl)	27.59 nmol/L (1.0 ug/dl)	19.31 nmol/L (0.7 ug/dl)	68.97 nmol/L (2.5 ug/dL)
ACTH range: 5-46pg/ml	2.43 pg/ml	7.47 pg/ml	4.5 pg/ml	8.65 pg/mL
* Profound suppression of HPA axis. Clobetasol was discontinued and patient received non-glucocorticosteroid topical treatment. Glucocorticoid replacement therapy begun. ** Suppression of HPA at 4, 14, 20 month following cessation of clobetasol therapy.				
Severe exogenous Cushing syndrome with the following:				
<ul style="list-style-type: none"> • Severe osteoporosis, with crushes of the thoracolumbar vertebrae, MRI demonstrated: (1) Grade 3 fracture with compression of the T12 vertebral body, resulting in narrowing of the vertebral canal and contact with the spinal cord; (2) Grade 2 fractures with anterior and superior compression at L1 and L3; (3) Grade 2 fractures with anterior compression at T5, T7 and T8; diffuse demineralization (according to Genant method of assessment). • Diabetes mellitus and obesity. • Sub-capsular cataract – treated with bilateral crystalline replacement. 				

SIDEBAR. The possibility of exogenous Cushing syndrome after treatments with topical corticosteroids was also emphasized in earlier syntheses. In an article from 2012 are depicted 5 cases of Cushing syndrome occurring after clobetasol-propionate topical treatments¹. The patient presented by us stands out by the severity of clobetasol-induced osteoporosis, suggesting a persistent and long-lasting exposure at high doses.

ACTH = corticotropin; HPA = hypothalamic-pituitary-adrenal.

Table 2. Case no. 2 description

MA, male, born in 1960, was evaluated in August 2015, referred by infectious disease specialist after a prolonged episode of severe cholangitis, with sepsis, resulting in 2 months (June-July 2015) anti-infectious and pharmacological GC therapy. Patient noticed in the period July – August 2015 low values of blood pressure (90/60 mmHg, significantly lower than his usual 130-140/85-90 mmHg). The patient is known from 2008 with asthma, managed with various forms of ICS – initially, budesonide for roughly 2 years, then with a stronger ICS, fluticasone propionate for 3 years. After October 2013 patient developed clinical signs suggestive of Cushing syndrome: plethora, purple striae on the abdomen and flanks, thinning of the skin with bruising, ecchymosis, centripetal fat redistribution and muscle wasting; diabetes mellitus (glycaemia between 150-200 mg/dL) was demonstrated. ICS were discontinued; prolonged action beta-2 agonist [indacaterol] started. 2015 August - Long Synacthen Stimulation Test [Synacthen-depot 1 mg, intramuscular] – at 6h – Cortisol = 1023.5 nmol/L (37.1 ug/dL); at 24h - Cortisol = 902 nmol/L (32.7 ug/dL); normal response definition: Cortisol = >550 nmol/L (>19.9 ug/dL).					
Hormonal testing (blood, 8AM)	August 2013 ^a	1 st visit – Aug 2015 ^b	2 nd visit – Feb 2017 ^c	3 rd visit – May 2017 ^d	4 th visit – Nov 2017 ^e
Cortisol – range: 101-535 nmol/L (3.7-19.4 ug/dl)	25.1 nmol/L (0.9 ug/dl)	287 nmol/L (10.4 ug/dl)	26.9 nmol/L (0.97ug/dl)	70.7 nmol/L (2.56 ug/dl)	180.8 nmol/L (6.55 ug/dL)
ACTH range: 5-46 pg/ml	5.48 pg/ml	31.6 pg/ml	<1 pg/ml	9.98 pg/ml	28.7 pg/mL
DHEA-S range: 49-362 pg/ml	-	27.5 ug/dl	20.3 ug/dl	-	26.4 µg/dL
Androstenedione range: 0.64-2.97 pg/ml	-	0.62 ng/ml	-	-	-
Renin range: 4.4-46.1 pg/ml	-	14 uU/ml	--	-	-

^a Two years before referral – tests suggestive of adrenal suppression preceding the assumed adrenal crisis during the sepsis.
^b One month after presumed adrenal crisis. Tests indicate a normal cortisol response (i.e. >20 ug/dL 24h after Synacthen), but a low level of adrenal androgens (AA). Low AA suggests relative AI². Dissociation between GC and AA might be generated by sepsis³.
^c In February 2017 clinical exam revealed findings suggesting of recurrent exogenous Cushing syndrome: muscular wasting, weight gain with fat redistribution, facial plethora, persistently high BP values, and high self-monitoring glycaemia (170-250 mg/dL). We found out about the use of nasal betamethasone with an intensification of self-administration suggesting overtreatment in the last 6 months. Betamethasone stopped.
^d HPA function was still subnormal, with low cortisol and inadequately normal ACTH - tertiary hypoadrenalism. GC replacement therapy begun - prednisone 5 mg/day.
^e In November 2017, 9 months after nasal betamethasone was stopped, HPA axis function was still impaired; the control of diabetes was improved - Glycaemia= 105 mg/dL, HbA1c = 6.1%. The GC replacement therapy was gradually suspended, maintaining CS supplementation in stress and re-test HPA-axis after 3 months.

SIDE BAR. A case of Cushing syndrome following ICS, as we presented here, was reported in 2013, where concomitant use of intranasal GC played an important role, too⁴.

GC = glucocorticoid; ICS - inhaled corticosteroid; ACTH = corticotropin; DHEA-S = dehydroepiandrosterone-sulfate; HPA = hypothalamic-pituitary-adrenal; HbA1c = Glycated hemoglobin.

LOCAL (COMPARTMENTAL) GLUCOCORTICOID ADMINISTRATION – ENDOCRINOLOGIST MINI-REVIEW

According to the pharmaceutical route of administration glucocorticoid (GC) therapy can be divided in: (a) systemic: oral, intravenous, intramuscular, and subcutaneous; (b) local or compartmental: topic (cutaneous, nasal, ophthalmic); inhaled; intraarticular. The therapeutic index for GC depends on the systemic absorption

of the drug, the metabolism (renal and/or hepatic clearance) and the degree of plasma protein binding.

Topical GC are used for a large spectrum of dermatological conditions and show a great variability in terms of bioavailability and pharmacokinetics (e.g. the fluorinated compounds, dexamethasone, triamcinolone, betamethasone, and beclomethasone are better absorbed through skin than the unfluorinated agents like hydrocortisone). Topical GC can be classified according to their potency and the capacity to inhibit HPA axis - Table 3 [based on *World Health Organization* (WHO) classification]. As a rule, higher dermatological potency will result in higher degree of HPA axis suppression and risk for adrenal insufficiency (AI). Super-active agents such as clobetasol ointment 0.05% can produce HPA suppression at doses as low as 2g/day and can result in Cushing syndrome at doses larger than 50 g/week (our patient in case no. 1 using 200 g/week). Pharmacological estimation showed that daily topical use of 20 mg clobetasol (= 40 g ointment clobetasol-propionate 0.05%) have the same systemic effect as the daily oral dose of 60 mg prednisone. Accordingly, therapy with clobetasol should not exceed 50 g/week, no longer than 2 weeks on a row.

Children showed a greater sensibility with HPA suppression demonstrated at doses of 14 g/week clobetasol-propionate or 49 g/week betamethasone-dipropionate⁵. There are reported an increasingly number of cases with HPA axis severely suppressed. In our patient (case no. 1), AI persisted even after 20 months since clobetasol suspension.

Inhaled corticosteroids (ICS), are pivotal to achieve asthma control in both children and adults. In Ta-

Table 3. Topical synthetic GC potency and capacity to inhibit HPA axis

Class	Dermatological potency	HPA-suppression	Examples
Class I [WHO – Ultra High]	SUPER ACTIVE (SUPER POTENT)	+++++	Clobetasol-propionate cream 0.05% Diflorasone diacetate ointment, 0.05% Betamethasone-dipropionate-glycol 0.05%
Class II-III [WHO – High]	HIGH POTENCY	++++	Betamethasone-dipropionate ointment 0.05% Fluocinonide cream, ointment or gel, 0.05% Triamcinolone acetonide ointment 0.5%
Class IV-V [WHO – Moderate]	MEDIUM STRENGTH	+++	Betamethasone-valerate cream 0.1% Fluocinolone acetonide cream 0.025% Triamcinolone acetonide lotion 0.1% Hydrocortisone 17-valerate cream 0.2%
Class VI-VII [WHO - Low]	LOW POTENCY	++	Betamethasone-valerate cream 0.05% Fluocinolone acetonide solution 0.01% Betamethasone valerate lotion 0.05% Methylprednisolone acetate cream 0.25% Hydrocortisone acetate cream 0.5% 1.0%

Table 4. Classification of ICS according with HPA suppression^{6,7}

ICS	Asthma potency	HPA-suppression	Daily dose [ug] suppressing cortisol 20%*	Equivalent dose (ug/day)		
				low	medium	large
Fluticasone - propionate	+++++	+++++	900	100-250	250-500	>500
Mometasone - furoate	++++	++++	660	200	200-400	>400
Beclomethasone - dipropionate	++	+++	500	100-200	200-400	>400
Budesonide	+	++	600	200-400	400-800	>800
Ciclesonide	+++	-	1200	80-160	160-320	>320

* NOTE: Therapeutic index is defined as the dose that produces 20% cortisol suppression divided by the therapeutic dose – the higher is this index the lower is the risk that ICS produces systemic effects.
ICS = inhaled corticosteroid; HPA = hypothalamic-pituitary-adrenal axis.

ble 4 ICS are sorted according with potency and HPA suppression. One ICS with higher potency needs lower inhaled daily dose for equivalent efficacy.

The schematic pharmacokinetic of ICS: (a) - 60-90% of the inhaled drug remains in pharynx and it is swallowed; from gut, it is absorbed and inactivated in liver at the first-pass by enzymes linked with CYP3A². Inhibitors for CYP3A cytochrome increase the GC levels and amplifies systemic effects (moderate inhibitors, e.g. diltiazem; tibolone; dronedarone; amiodarone; mifepristone; erythromycin; fluconazole; grapefruit juice, and strong inhibitors, e.g., ceritinib; indinavir; clarithromycin; itraconazole; ketoconazole). Ciclesonide, fluticasone and mometasone are virtually completely metabolized, while 11% budesonide and 20-40% beclomethasone escapes the first-pass and reach the systemic circulation. Therefore, it is better to select one ICS with greater hepatic clearance. (b) - 10-40% of the inhaled drug reach the respiratory system and then delivered into circulation (e.g. 20% of inhaled fluticasone).

In terms of prednisolone equivalency, adrenal suppression with a large dose of budesonide (1000 ug per day) was estimated to be as high as with 8.7 mg of prednisolone⁸. Important dose-effect relationship between ICS and urinary cortisol suppression was documented with beclomethasone (8.4% per 100 µg; p =0.029), followed by fluticasone (3.2% per 100 µg; p <0.001), and budesonide (3.1% per 100 µg; p= 0.001); no significant suppression was associated with ciclesonide⁹. Pharmacological properties of ciclesonide made it the safest ICS [i.e. - 160-600 ug/day ciclesonide didn't affect cortisol level]¹⁰. The highest risk for adrenal suppression is encountered in children, especially when ICS was fluticasone¹¹, if the ICS were used for more than

6 months and if were associated with hypoglycemia, mental impairment, fatigability, anorexia, Cushingoid appearance or impaired linear growth.

ENDOCRINE EFFECTS OF COMPARTMENTAL GC ADMINISTRATION

The undesired side effects after compartmental GC administration could be local, specific to type of therapy and systemic, common to all types. The endocrine systemic effects are: (1) HPA axis suppression; (2) exogenous Cushing syndrome.

(1) HPA axis suppression and adrenal insufficiency

GC therapy is the most common cause of adrenal insufficiency (AI). GC administration decrease hypothalamic corticoliberin (CRH), as well as pituitary adrenocorticotrophic hormone (ACTH) production and induce adrenocortical cells functional inhibition and atrophy. GC use in a dose larger than the equivalent of 20 mg prednisone/day for more than 3 weeks can induce HPA-axis suppression. When are taken at the bed-time even doses of ≥5 mg prednisone/day can induce suppression¹². Adrenal suppression was documented both after oral GC and after ICS¹³. In a study of HPA function after systemic GC use in 3166 patients, the median prevalence of AI was 37% and the recovery of the normal function occurred in 58.8% patients 1-2 years after systemic GC withdrawal¹⁴. In a recent study with 404 patients taking oral, topical, intranasal or inhaled GC therapy, 33.2% had a subnormal short Synacthen stimulation test (SST) response¹⁵. In a meta-analysis conducted on 3753 subjects exposed to

Table 5. Prediction of HPA axis suppression and prevention factors

	HPA axis suppression risk	Prevention
COMMON FACTORS		
General aspect	Cushingoid features → HPA axis suppression is very likely	Absence of Cushingoid features → HPA suppression is unlikely
Daily dose	Best way to predict HPA suppression	Use of minimal doses
Route of administration	<input type="checkbox"/> Continuous use increases the risk <input type="checkbox"/> Several daily administrations increase risk	<input type="checkbox"/> If possible – pulsatile or alternant therapy <input type="checkbox"/> Unique administration, in the morning
Duration and cumulative dose	Weak determinants of the risk	No suppression for shorter periods than 2 weeks
SPECIFIC FACTORS FOR INHALED CORTICOSTEROIDS		
Duration	>6 month, with high doses	<input type="checkbox"/> Minimal effective dose
Combined administration	Concomitant use of other kinds of GC (e.g. systemic GC in asthma exacerbation or nasal for rhinitis)	<input type="checkbox"/> Optimization of compliance <input type="checkbox"/> Mouth and pharynx washing <input type="checkbox"/> Association of other bronchodilator agents
Low weight patients	<input type="checkbox"/> Body mass index <15 percentile for age <input type="checkbox"/> Children and teenagers	<input type="checkbox"/> Non-pharmacological methods (vaccinations, avoidance of allergens)
SPECIFIC FACTORS FOR TOPICAL GC		
High doses of active and super active derivate	<input type="checkbox"/> With class I (clobetasol) adrenal suppression can occur in 3 weeks. <input type="checkbox"/> Ointment has higher risk than any other pharmaceutical form	<input type="checkbox"/> Lowest possible dosage <input type="checkbox"/> Decrease doses in children (1/5; 2/5; 1/3 - of the dose required to adults in toddlers, children and teenagers, respectively)
The application surface	<input type="checkbox"/> Large areas <input type="checkbox"/> Regions with high permeability <input type="checkbox"/> Occlusive therapy (increases potency by 100 times) <input type="checkbox"/> Children, old people, hepatic failure	<input type="checkbox"/> Avoidance of areas with high absorption rate (face, genitals) or deteriorated skin

GC = glucocorticoids; HPA = hypothalamic-pituitary-adrenal axis.

systemic or local GC, the percentages of tertiary AI were: 48.3% - after systemic GC; 6.8% - after ICS; 4.7% - after topical corticosteroids; 4.2% - after intranasal GC; 52.2% - after intraarticular GC¹⁶. The combined GC therapy (i.e. ICS and intranasal GC) resulted in a higher risk of HPA suppression (e.g. an 19% excess). In a recent article, 61% of patients with adrenal suppression after systemic GC had normal SST after 2 years¹⁷. In this study, age, gender, body mass index, indications for GC use, and basal corticotropin levels were not predictive of HPA axis recovery; one useful finding was that early morning cortisol of 8.8µg/dL predicted a positive SST response.

Specific factors for prediction of HPA suppression after local GC are in Table 5.

The basic principle for the GC withdrawal is to avoid sudden discontinuation. Instead, the daily dose gradually decreases with 2.5 mg prednisone/day every 3-4 days, until are reached physiological doses (= equivalent of 5-7.5 mg prednisone/day). Estimations are based on physiological cortisol production 5.7-7.4 mg/m²/day, corresponding to a daily dose of 10-15 mg hydrocortisone/m²/day, orally or 6-8 mg/m²/day, intravenous, lower than previously thought¹⁸. After these doses are reached, taper slower, 1 mg prednisone every 2-4 weeks

until cessation OR testing with SST and stop the GC whenever the test is normal. Proposed algorithm for HPA assessing for practitioners using GC therapy – see Table 6.

Adrenal crisis is a medical emergency. Adrenal crisis in tertiary AI occur after abrupt discontinuation of GC. The frequency of adrenal crisis is higher in tertiary AI, i.e. 15.1 cases in 100 patients/year, than in primary AI, 5.2 cases, or secondary AI, 3.6 cases in 100 patients/year²⁰. In Table 7 are presented the updated criteria for diagnosis of adrenal crisis and basic treatment measures.

(2) Exogenous Cushing syndrome

Exogenous Cushing syndrome is the most common form of Cushing syndrome. The main features and resemblances with endogenous Cushing syndrome are listed in Table 8. In children, first significant undesired effect associated with GC use is diminished linear growth, encountered even with short-term ICS (i.e. 7 days) if high-doses are used²².

Glucocorticoid-induced osteoporosis (GIO) is one of most important feature of exogenous Cushing syndrome and the most frequent form of iatrogenic osteoporosis. GC effects on bone result in 2 phases: first

Table 6. Algorithm for HPA-suppression during local GC administration^{15,17,19}

Step I – Risk estimation	
Who to screen?	<ul style="list-style-type: none"> ○ Cushingoid appearance, OR ○ suspected AI: weakness, anorexia, nausea, diarrhea, abdominal pain, morning headaches, myalgia, arthralgia, hypoglycemia, hypotension, OR ○ large ICS doses (i.e. fluticasone or mometasone >400 ug/day; budesonide or beclomethasone >800 ug/day) – for >3 weeks in last 3 months ○ large topical corticosteroids doses– clobetasol 0.05% >2 g/day or treatment over 2 weeks with >100 g clobetasol /week, OR ○ association with oral GC >2 weeks continuously or >3 weeks in last 6 months, OR ○ association with CYP450 3A inhibitors, OR ○ yearly for any patient using large doses of compartmental GC
How to screen?	<ul style="list-style-type: none"> ☐ Morning 8- 9AM serum cortisol* - A baseline cortisol result below 100 nmol/l is considered highly indicative of adrenal insufficiency ☐ Free urinary cortisol - [normal range in children = 5.5-74 nmol/L (2-26 ug/L); in adults = 14-152 nmol/L (5-55 ug/L)].
Step II – Normal functioning hypothalamic-pituitary-adrenal (HPA) axis	
Cortisol > 348 nmol/L (12.6 ug/dL)	→ rules out significant suppression of HPA axis; no need for oral substitution therapy or GC supplementation before major surgery. If the manifestation of adrenal deficit is persistent → perform SST
Step III – Equivocal functioning HPA axis	
Cortisol = 35-348 nmol/L (1.26-12.6 ug/dL)	→ Perform 250 ug short Synacthen stimulation test (SST). Inadequate = Cortisol < 550 nmol/L (19.8 ug/dL) → <ul style="list-style-type: none"> ☐ begin oral substitution and GC supplements before major surgery; ☐ reduce doses of compartmental GC; ☐ repeat cortisol testing in 3 months.
Step IV - Suppressed HPA axis	
Cortisol <35 nmol/L (<1.26 ug/dL)	→ Diagnose adrenal insufficiency - no need to perform SST <ul style="list-style-type: none"> ☐ start substitution therapy or GC; supplements before major surgery; ☐ reduce doses of compartmental GC; ☐ repeat cortisol testing in 3 months. <p>Note! In patients treated with local GC even excessive amounts, resulting in Cushingoid traits might not result in sufficient serum concentration in stress situations. That's why local GC withdrawal needs the concomitant use of oral GC with replacement dose and GC supplementation in stressful events.</p>
* NOTE. Synacthen is not available in Romania, and insulin-induced hypoglycemia test (ITT), the gold standard for assessing the HPA axis, is cumbersome to use outside endocrinological units. This is the reason why we searched validated basal tests for rapid detection and/or referral of adrenal suppression. HPA = hypothalamic-pituitary-adrenal axis; GC = glucocorticoids; AI = adrenal insufficiency; ICS = inhaled corticosteroids; SST = short Synacthen stimulation test.	

Table 7. Definitions, severity and treatment of adrenal crisis²¹

Definition	<p>A) Major impairment of general health with at least two of the following:</p> <ol style="list-style-type: none"> 1. Hypotension (systolic blood pressure <100 mmHg) 2. Nausea or vomiting 3. Severe fatigue 4. Fever 5. Somnolence 6. Hyponatraemia (≤ 132 mmol/l) or hyperkalaemia 7. Hypoglycaemia <p>B) Prompt clinical improvement after parenteral hydrocortisone</p>
Severity	<p>Grade 1 – outpatient care only</p> <p>Grade 2 – hospital care (general ward), no need for intensive care</p> <p>Grade 3 – admission to intensive care unit</p> <p>Grade 4 – death from adrenal crisis (with or without GC administration)</p>
Treatment confirmed or suspected adrenal crisis [treatment is started before biochemical confirmation]	<p>→ Establishing an intravenous route</p> <p>→ Sampling the blood for glycaemia, Na, K, hemoleucogram, cortisol</p> <p>→ Hydrocortisone: 100 mg bolus given immediately followed by 200 mg/ day as continuous infusion or frequent i.v./ i.m. boluses (50 mg) every 6 h</p> <p>→ Intravenous substitution of fluids: 1000 ml of 0.9% sodium chloride during the first 60 min + glucose 5% [if hypoglycaemia]; further fluid administration (0.9% sodium chloride) guided by individual needs as assessed clinically or by central venous pressure and avoiding overload. The quantity infused depends on evolution of blood-pressure, heart rate, diuresis, ionogram, central venous pressure and pulmonary auscultation</p> <p>→ Depending on the severity of the crisis and on the intercurrent illness [e.g. low-dose heparin; antibiotic treatment]</p>

Table 8. Cushing syndrome – comparison between endogenous and exogenous types

Exclusively in exogenous Cushing	More frequent in endogenous Cushing
Intracranial hypertension	Arterial hypertension
Glaucoma; cataract	Acne and hirsutism
Aseptic bone necrosis	Menstrual abnormalities
Pancreatitis	Striae and ecchymosis
Panniculitis	Plethoric facies
In both endogenous and exogenous Cushing	
Central obesity and fat redistribution. Peripheral myopathy and cardiomyopathy	
Osteoporosis. Atherosclerosis and thrombosis. Peptic ulceration and digestive bleeding	
Glucose intolerance and diabetes mellitus. Sodium retention and potassium excretion	
Psychological changes – lability, insomnia, psychosis, cerebral atrophy	
Delayed healing. Immunosuppression and lymphopenia; undercurrent infections	
Diminution of height growth in children	

Table 9. Treatment of GIO in adults^{27,28}

FRAX GC-adjusted*	ATTITUDE
CATEGORY - Adults ≥40 years of age, with GC therapy for ≥ 3 months	
Low fracture risk - FRAX 10-year risk of major osteoporotic fracture** <10% and risk of hip fracture ≤1%	Prefer optimize calcium intake (0.8-1 g/day) and vitamin D intake (600-800 IU/day) and lifestyle modifications (balanced diet, smoking cessation, regular weight-bearing or resistance training exercise, limiting alcohol to 1-2 alcoholic beverages/day) over treatment with bisphosphonates, teriparatide, denosumab, raloxifene.
Moderate fracture risk - FRAX 10-year risk of major osteoporotic fracture 10-19% or risk of hip fracture 1-3%	ORAL BISPHOSPHONATE. Based on cost-effectiveness criteria alendronate and risedronate are preferred. Prefer an oral bis-phosphonate over IV bisphosphonates, teriparatide, denosumab. If oral bisphosphonates are not appropriate , in order: (1) intravenous (IV) bisphosphonates – acid zoledronic; (2) teriparatide***; (3) denosumab (4) raloxifene.
High fracture risk: Very high-dose GC**** OR FRAX risk of major osteoporotic fracture ≥20% or risk of hip fracture ≥3% OR prior osteoporotic fracture OR hip/spine bone mineral density (BMD) T score ≤ -2.5 in men age ≥50 years or post-menopausal women.	ORAL BISPHOSPHONATE. Treat with an oral bisphosphonate over IV bisphosphonates, teriparatide, denosumab, or raloxifene. If oral bisphosphonates are not appropriate , in order: (1) IV bisphosphonates [higher risk profile for IV]; (2) Teriparatide [cost and burden of injections]; (3) Denosumab [lack of safety data in people treated with immunosuppressive agents]; (4) Raloxifene, for postmenopausal women [lack of adequate data on benefits (impact on risk of vertebral and hip fractures in GC users) and potential harms (clotting risks, mortality)].
SPECIAL CASES IN THIS CATEGORY	
Adults age ≥40 years continuing GC treatment who have had a fracture that occurred after ≥18 months of treatment with an oral bisphosphonate or who have had a significant loss of BMD (≥10%/year) → Treat with another class of OP medication (teriparatide or denosumab; or, consider IV bisphosphonate).	
Adults age ≥40 years who have completed 5 years of oral bisphosphonate treatment and who continue GC treatment and are assessed to be at moderate-to-high risk of fracture → Continue active treatment , with an oral bisphosphonate beyond 5 years or switch to IV bisphosphonate.	
CATEGORY - Adults <40 years of age, with GC therapy for ≥3 months	
Low risk = None of above risk factors other than GC	Optimize calcium and vitamin D intake and lifestyle modifications over treatment with bisphosphonates, teriparatide, or denosumab.
Moderate fracture risk = Hip or spine BMD Z score < -3 OR rapid bone loss (≥10% at the hip or spine over 1 year) + continuing GC at ≥7.5 mg prednisone/day for ≥6 months	TREAT WITH AN ORAL BISPHOSPHONATE over calcium and vitamin D alone. Oral bisphosphonate over intravenous (IV) bisphosphonates, teriparatide, or denosumab [oral bisphosphonates preferred for safety, cost, and because of lack of evidence of superior antifracture benefits from other medications].
High fracture risk = Prior osteoporotic fracture(s)	If oral bisphosphonates are not appropriate , in order of preference: (1) IV bisphosphonates; (2) Teriparatide; (3) Denosumab. Estimate the need for sexual hormones therapy in premenopausal women with amenorrhea and in men with hypogonadism.
* FRAX-GC = FRAX-glucocorticoid adjusted risk - increase the risk generated with FRAX - by 1.15 for major osteoporotic fracture and 1.2 for hip fracture if GC treatment is equivalent >7.5 mg prednisone/day.	
** Major osteoporotic fracture includes fractures of the spine, hip, wrist, or humerus.	
*** Teriparatide is recommended for the failure of bisphosphonate therapy = the occurrence of extra-vertebral fractures or ≥2 vertebral fractures after 12 months of bisphosphonate therapy.	
**** Very high-dose GC treatment = prednisone ≥30 mg/day and a cumulative dose of >5 g in the past year.	

rapid bone mass, 12% in the first 3-12 months followed by a phase of slower bone mass loss, of 2-15% every 12 months. GIO can occur not only after systemic CS, but with ICS²³ and topical GC²⁴. One short guide for prevention and treatment of GIO is presented Table 9.

CONCLUSION

It is estimated that approximately 6% of hospitalized patients have GC-induced tertiary AI²⁵. In this article, we intended to draw attention to the endocrine effects generated by compartmental GC treatments. GC preparations with the so-called local effects (e.g. topical, inhaled, intra-articular) have been shown to exert systemic effects that can not be neglected, the most important for endocrinologists being exogenous Cushing syndrome and glucocorticoid-induced AI. One meta-analysis showed evidence of AI following low doses and short durations of GC (<5 mg prednisolone

equivalent dose/day, <4 weeks of exposure, cumulative dose <0.5 g, and following tapered withdrawal)²⁶. There is no clinical guidance for AI occurring after systemic CS and even lesser agreements for AI induced by local GC. This data must lead the practitioners using topical, inhaled, or intra-articular GC to an increased alertness level toward the possibility that even compartmental administration could cause significant systemic endocrine effects.

Compliance with ethics requirements:

The authors declare no conflict of interest regarding this article.

The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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