Ipposurrenalismo secondario: diagnosi e terapia

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Conflitti di interesse

Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:

- Shire
- Novartis

LA DIAGNOSI

Epidemiologia

Con 150-280 casi per milione è la forma più frequente di iposurrenalismo

Prevalente nelle donne

Picco di età nella sesta decade

Eziologia

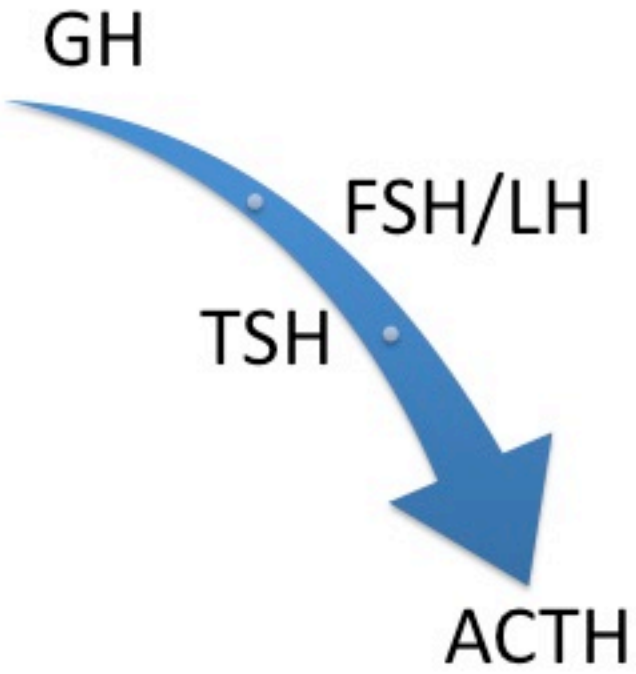


Table 1. Etiology of Central Hypoadrenalism

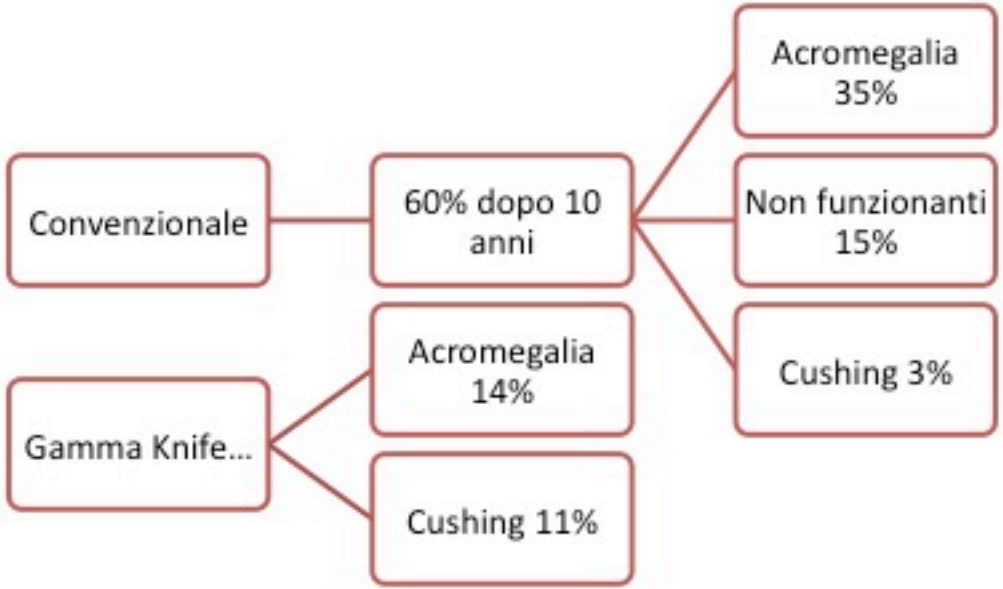
Genetic *Isolated ACTH deficiency* POMC mutation / *clearance defect (can be acquired* (10 Mu TBX19, pos *Associated with other pituitary deficiencies* PROP1 (22), LHX3 (23), LHX4 (24), HESX1 (25), OTX2 mutations Congenital Septo-optic dysplasia (without HESX1 mutation) Rathke's cleft cysts Tumoral Craniopharyngioma (up to 90% cases)(29) Non-functioning pituitary adenoma (50% pre-op, 75% post-op)(104) Functional pituitary adenomas Pituitary metastases Other Tumors (e.g. germinoma / optic glioma / astrocytoma / meningioma) Iatrogenic Exogenous glucocorticoids (oral, intravenous, inhaled, intramuscular, topical, intranasal) Pituitary surgery Cranial irradiation Post-treatment for hypercortisolism (pituitary or adrenal surgery, see Table 3)	Infiltrative Neurosarcoidosis Histiocytosis Haemochromatosis Inflammatory / infection Hyp / mi Pos tub Miscellaneous Idiopathic Empty sella syndrome Pituitary apoplexy (20% if surgically managed)(105) Traumatic brain injury (12%)(30) Subarachnoid hemorrhage (14% acute, 6% persistent)(106) Sheehan's syndrome

ACTH FIRST

ACTH FIRST

Una causa, una probabilità

Radioterapia



Trattamento steroideo

J Endocrinol Invest (2017) 40:1175–1181
DOI 10.1007/s40618-017-0691-1

SHORT REVIEW

The unresolved riddle of glucocorticoid withdrawal

F. Guerrero Pérez[1] · A. P. Marengo[1] · C. Villabona Artero[1]

- Global incidence of 31.7%.
  - 4.2% for nasal GC, 4.7% for topical administration, 7.8% for inhalation,
  - 48.7% for oral GC to 52.2% for intra-articular treatment.
- AI occurred on a scale of 6.8% of asthmatic patients using only inhalation GC to 60% of patients with hematological malignancies.

There are several factor involved in adrenal function after GC use and it is not possible an accurate prediction of the adrenal status in all patients based on the patient history of GC therapy

Starting dose of prednisone (or equivalent)	Progressive decrease of daily dose
>40 mg/day	5–10 mg/day every 1–2 weeks
20–40 mg/day	5 mg/day every 1–2 weeks
10–19 mg/day	2.5 mg/day every 2–3 weeks
5–9 mg/day	1 mg/day every 2–4 weeks
<5 mg/day	0.5 mg/day every 2–4 weeks

- Sono oggi disponibili anticorpi monoclonali anti-CTLA-4, anti-

- ipotiroidismo centrale: ~ 87%;
- ipogonadismo ipogonadotropo: ~ 85%;
- iposurrenalismo secondario: ~ 73%;
- deficit di GH: ~ 25%;
- ipo- (più spesso) o iperprolattinemia: ~ 25%.

coll hanno riportato un **rischio relativo cumulativo** di ipofisi
0.00001).

In circa la metà dei casi, le disfunzioni tiroidea e gonadica possono essere reversibili, con una mediana di 10 e 13 settimane rispettivamente in uno studio, mentre l'iposurrenalismo è quasi sempre permanente, in maniera purtroppo non prevedibile.

Vincenzo Di Donna (dottdido@libero.it) & **Salvatore Maria Corsello**
UO di Endocrinologia, Università Cattolica del Sacro Cuore, Policlinico "A. Gemelli", Roma

La clinica

- In secondary adrenal insufficiency, the mineralocorticoid axis is intact; thus, postural hypotension and electrolyte abnormalities are less frequent.
- However, hyponatraemia can occur due to decreased inhibitory control of vasopressin secretion, effectively resulting in mild syndrome of inappropriate antidiuretic hormone secretion.
- Hyperpigmentation is absent because of reduced stimulation of skin MC1R by adrenocorticotropic hormone, giving the skin an alabaster-like appearance.
- Other pituitary axes might also be compromised, as might vision due to compression of the optic chiasm.

Diagnosis and management of adrenal insufficiency

Irina Bancos, Stefanie Hahner, Jeremy Tomlinson, Wiebke Arlt

Lancet Diabetes Endocrinol
2015; 3: 216–26

DELAYED DIAGNOSIS

ACTH Stimulation Tests for the Diagnosis of Adrenal Insufficiency: Systematic Review and Meta-Analysis

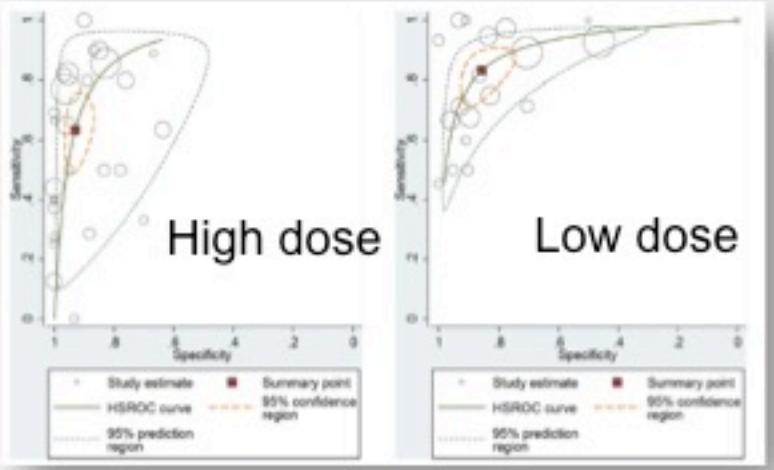
J Clin Endocrinol Metab, February 2016, 101(2):427–434

Table 1. Meta-Analysis Results: ACTH Stimulation Tests for the Diagnosis of Secondary Adrenal Insufficiency

	Estimate	95% CI
Adult High-Dose ACTH Stimulation Test		
Sensitivity	0.64	0.52–0.73
Specificity	0.93	0.89–0.96
Likelihood ratio for positive test	9.1	5.7–14.6
Likelihood ratio for negative test	0.39	0.30–0.52
Diagnostic odds ratio	23	13–42
Adult Low-Dose ACTH Stimulation Test		
Sensitivity	0.83	0.75–0.89
Specificity	0.86	0.78–0.91
Likelihood ratio for positive test	5.9	3.8–8.9
Likelihood ratio for negative test	0.19	0.13–0.29
Diagnostic odds ratio	30	18–50
Children High-Dose ACTH Stimulation Test		
Sensitivity	0.36	0.10–0.73
Specificity	0.99	0.81–0.99
Likelihood ratio for positive test	43.5	1–1891.2
Likelihood ratio for negative test	0.65	0.36–1.15
Diagnostic odds ratio	67	1–4152
Children Low-Dose ACTH Stimulation Test		
Sensitivity	0.69	0.28–0.93
Specificity	0.91	0.63–0.98
Likelihood ratio for positive test	7.7	1.3–44.8
Likelihood ratio for negative test	0.34	0.10–1.18
Diagnostic odds ratio	23	2–313

Table 2. ACTH Stimulation Tests for the Diagnosis of Secondary Adrenal Insufficiency Based on Cortisol Cutoff

Adults									
High-Dose ACTH Test					**Low-Dose ACTH Test**				
Cortisol Cutoff (nmol/liter)	LR+	LR−	Diagnostic OR	No. of Studies	LR+	LR−	Diagnostic OR	No. of Studies	*P* Value (for Difference)
500–30 minutes	6.3 (2.5–16)	0.32 (0.20–0.51)	20 (5–75)	6	NR	NR	NR	NR	NA
500-peak	12.4 (6.7–23.0)	0.48 (0.32–0.72)	26 (11–60)	14	7.1 (4.3–11.6)	0.21 (0.13–0.33)	34 (17–68)	11	631
550-peak	6.4 (3.4–12)	0.36 (0.21–0.61)	18 (8–43)	8	3.8 (1.5–9.4)	0.23 (0.11–0.49)	16 (6–40)	6	855
Children									
High-Dose ACTH Test					**Low-Dose ACTH Test**				
500-peak	15.96 (2.12–120.04)	0.37 (0.01–12.95)	40.67 (1.1–1424.1)	2	18.3 (2.04–164.72)	0.31 (0.5–1.9)	93.63 (14.6–620.1)	3	686
550-peak	6.1 (1.09–34.17)	0.78 (0.58–1.06)	7.96 (1.2–51.4)	2	4.3 (2.65–7.06)	0.2 (0.02–1.92)	24.8 (1.73–356.9)	2	494



ACTH Stimulation Tests for the Diagnosis of Adrenal Insufficiency: Systematic Review and Meta-Analysis

J Clin Endocrinol Metab, February 2016, 101(2):427–434

ITALIAN CHAPTER

High dose e low dose non sono differenti nel SAI

- Precedenti review indicavano una superiorità del low dose

La performance del test dipende dalla probabilità pre-test di malattia

- Mancano criteri validati
- Dipende dall'esperienza clinica

Un test negativo in un paziente ad alto rischio di SAI non riduce di molto la possibilità di malattia

Un test negativo in un paziente a basso rischio di SAI esclude la possibilità di malattia

In caso di test equivoci vi è indicazione all'ITT

www.associazionemediciendocrinologi.it
Breaking news
nr. 3 – marzo 2016
LE LINEE GUIDA DELL'*ENDOCRINE SOCIETY* PER L'INSUFFICIENZA SURRENALICA PRIMARIA
Responsabile Editoriale
Renato Cozzi

Nel PAI il test migliore è quello con ACTH

- 250 µg nell'adulto e nel bambino di età ≥ 2 anni; 125 µg nel bambino di età < 2 anni; 15 µg/kg nel neonato
- valutazione della risposta di cortisolo in termini di picchi a 30 o 60 minuti (considerata patologica se < 18 µg/dL, 500 nmol/L) (livello di evidenza 2, qualità ⊗⊗○○
- L'ACTH test con 1 µg è suggerito soltanto quando il farmaco per eseguire il test non è momentaneamente disponibile o per ragioni economiche (livello di evidenza 2, qualità ⊗⊗○○)

L'interpretazione dell'ACTH test può essere influenzata da condizioni che aumentano la cortisolemia, per aumento della *Cortisol-Binding Globulin* (CBG) (estrogeni, gravidanza, mitotane), o ridurla per riduzione della CBG (sindrome nefrosica, epatopatia, periodo post-chirugico o pazienti in terapia intensiva, infiammazione, disordini genetici rari)

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Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline

ACTH		
Insulin tolerance	Administer insulin, 0.05–0.15 U/kg iv. Sample blood at −30, 0, 30, 60, and 120 min for cortisol and glucose.	Glucose should drop <40 mg/dL (2.2 mmol/L). Peak cortisol should be >500–550 nmol/L (>18.1–20 μg/dL) depending on assay.
Corticotropin standard dose (250 μg)	Administer ACTH 1–24 (cosyntropin), 250 μg im or iv. Sample blood at 0, 30, and 60 min for cortisol.	Cortisol should be at 30 or 60 min >500–550 nmol/L (>18.1–20 μg/dL) depending on assay.
Corticotropin low dose (1 μg)	Administer ACTH 1–24 (cosyntropin), 1 μg iv. Sample blood at 0 and 30 min for cortisol.	Cortisol should be at 30 min >500 nmol/L (18.1 μg/dL) depending on assay.

- 1.1 We suggest measuring serum cortisol levels at 8–9 AM as the first-line test for diagnosing central AI. (2⊗○○○)
- 1.2 We recommend against using a random cortisol level to diagnose AI. (1⊗⊗○○)
- 1.3 We suggest that a cortisol level < 3 mcg/dL is indicative of AI and a cortisol level > 15 mcg/dL likely excludes an AI diagnosis. (2⊗○○○)
- 1.4 We suggest performing a corticotropin stimulation test when morning cortisol values are between 3 and 15 mcg/dL to diagnose AI. Peak cortisol levels < 18.1 mcg/dL (500 nmol/L) at 30 or 60 minutes indicate AI. (2⊗⊗○○)
- 1.5 We suggest that clinicians perform biochemical testing for the HPA axis at least 18–24 hours after the last HC dose or longer for synthetic GCs. (2⊗⊗○○)

Caso clinico 1

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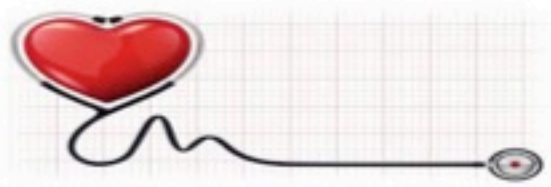
Alice 24 anni

Visita URGENTE

per astenia ingravescente e febbricola



PAO 100/60 mmHg, Fc 72’R

peso 52 kg, h 1.72 m, vita 60 cm

Lieve pallore del viso

EOC, EOP, EOA indifferenti

Anamnesi

- ✓ Superati i comuni esantemi infantili.
- ✓ Menarca a 14 anni, eumenorrea e dismenorrea, in E-P da 4 anni.
- ✓ Da circa **1 anno** astenia ingravescente (difficoltà a studiare, ad uscire di casa, a praticare qualsiasi attività fisica), febbricola serale.
- ✓ Da **qualche mese** poliuria (apparentemente non associata a polidipsia).
- ✓ Nega traumi cranici.
- ✓ Non assume farmaci (tranne paracetamolo alla sera).

Qualche segno o sintomo sospetto ?

Table 2. Clinical Manifestations of Hypopituitarism

Symptom/Sign	Pituitary Trophic Hormone Deficiency
General	
Fatigue, weakness	ACTH, TSH, LH/FSH, GH
Weight gain	TSH
Weight loss	ACTH
Decreased exercise capacity	ACTH, TSH, LH/FSH, GH
Impaired sleep quality	TSH, LH/FSH, GH
Depression	TSH, GH, LH/FSH
Cognitive decline	ACTH, TSH, ?GH
Cold intolerance	TSH
Skin	
Pallor	ACTH, LH/FSH
Dry skin	ACTH, TSH
Thinning hair, loss of body hair	ACTH, TSH, LH/FSH
Cardiovascular/metabolic	
Hypertension	TSH, GH
Hypotension, particularly orthostatic	ACTH
Bradycardia	TSH
Decreased lean body mass, increased fat mass	GH
Hyperlipidemia	TSH, GH
Insulin resistance, impaired glucose tolerance	TSH, GH
Hypoglycemia	ACTH
Impaired cardiac function	ACTH, TSH, GH
Premature atherosclerosis	TSH, GH
Pulmonary	
Shortness of breath, dyspnea on exertion	ACTH, TSH
Gastrointestinal	
Anorexia	ACTH
Nausea/vomiting	ACTH
Diarrhea/loose stools	ACTH
Constipation	TSH
Musculoskeletal	
Muscle weakness	ACTH, TSH, LH/FSH, GH
Osteoporosis, fractures	ACTH, TSH, LH/FSH, GH
Renal	
Increased thirst	ADH
Polyuria, nocturia	ADH
Reproductive	
Oligo/amenorrhea	ACTH, TSH, LH/FSH
Erectile dysfunction	LH/FSH
Low libido	LH/FSH
Hot flashes	LH/FSH
Infertility	LH/FSH
Vaginal dryness	LH/FSH

Esami di I livello

RBC 5.71, WBC 7.08, PLTs 284, Hb 15, Hct 40%

Na 138 mmol/l, K 4.0 mmol/l

Cortisolo 9.4 µg/dl (v.n. 6.2-19.4 µg/dl)

ACTH 17.7 pg/ml (v.n. < 46 pg/ml)

DHEAS 234 µg/l (v.n 100-4000)

Aldosterone 158 pg/ml (v.n. 70-350 pg/ml)

PRA 1.65 ng/ml/h (v.n. 1.31-3.95 ng/ml)

Avreste fatto tutto ?

Avreste fatto altro ?

1.0 Diagnosis of hypopituitarism

Central adrenal insufficiency

1.1 We suggest measuring serum cortisol levels at 8–9 AM as the first-line test for diagnosing central adrenal insufficiency (AI). (2|⊕◯◯◯)

1.2 We recommend against using a random cortisol level to diagnose AI. (1|⊕⊕◯◯)

1.3 We suggest that a cortisol level <3 μg/dL is indicative of AI and a cortisol level >15 μg/dL likely excludes an AI diagnosis. (2|⊕◯◯◯)

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DHEAS 234 µg/l (v.n 100-4000)

Aldosterone 158 pg/ml (v.n. 70-350 pg/ml)

PRA 1.65 ng/ml/h (v.n. 1.31-3.95 ng/ml)

Esami di II livello

Test hCRH (100 µg e.v. tempo 0'):

Cortisolo 4.8-6.0-9.7-13.4-17.5-15.7-13.5 µg/dl (135-166-268-372-484-435-373 nmol/l)

ACTH 6.6-7.4-53.6-46.2-34.9-27.6 pg/ml

RMN ipofisi con mdc

Avreste fatto tutto ?

Avreste fatto altro ?

1.4 We suggest performing a corticotropin stimulation test when morning cortisol values are between 3 and 15 μg/dL to diagnose AI. Peak cortisol levels <18.1 μg/dL (500 nmol/L) at 30 or 60 minutes indicate AI. (2|⊕⊕◯◯)

1.5 We suggest that clinicians perform biochemical testing for the hypothalamic-pituitary-adrenal (HPA) axis at least 18–24 hours after the last hydrocortisone (HC) dose or longer for synthetic glucocorticoids (GCs). (2|⊕⊕◯◯)

CRH Test

(hCRH, oCRH; 1 µg/Kg , 100 µg i.v.)

*Low sensitivity

*Side effects: transient facial flushing, altered sense of taste

*Drugs interference: glucocorticoids, antidepressant, E-P, naloxon, vasopressin

Normality:
% cortisol vs baseline (1.5) or
peak cortisol > 18-20 µg/dl (500-550 nmol/l)
peak ACTH > 100 pg/ml (33 pmol/l)

Schlaghecke et al 1992; NEJM 326: 226-230
Schmidt et al 2003; JCEM 88: 4193-4198
Grossman AB 2010; JCEM 95: 4855-4863
Crowley RK et al 2014; JCEM 99: 4027-4036

«Insufficienza surrenalica secondaria parziale»

SI?

NO?

Rivalutazione

… dopo sospensione E-P …

Cortisolo 17.8 µg/dl (v.n. 6.2-19.4 µg/dl)

Osmolarità P 287 mOsm, osmolarità U 468 mOsm (diuresi 1500 cc)

Na 141 mmol/l, K 4.1 mmol/l

Test ACTH 1 µg: cortisolo 17.9-23.0 µg/dl (493-634 nmol/l)

- ✓ Paziente a bassissimo **rischio per SAI**
- ✓ Interpretazione **esami di I livello** in corso E-P
- ✓ Impiego di **esame di II livello** non appropriato

Risultato = diagnosi errata ….

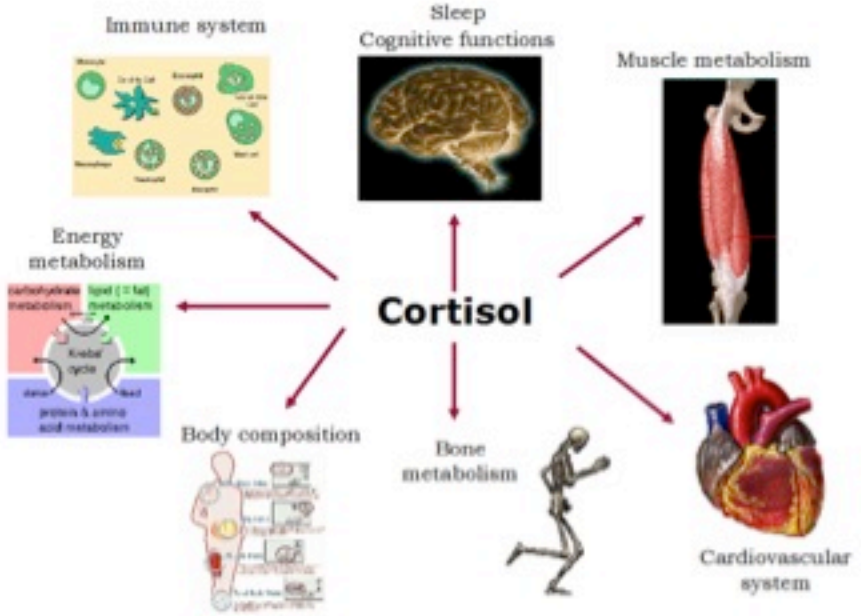
= rischio di terapia GC ad vitam ?

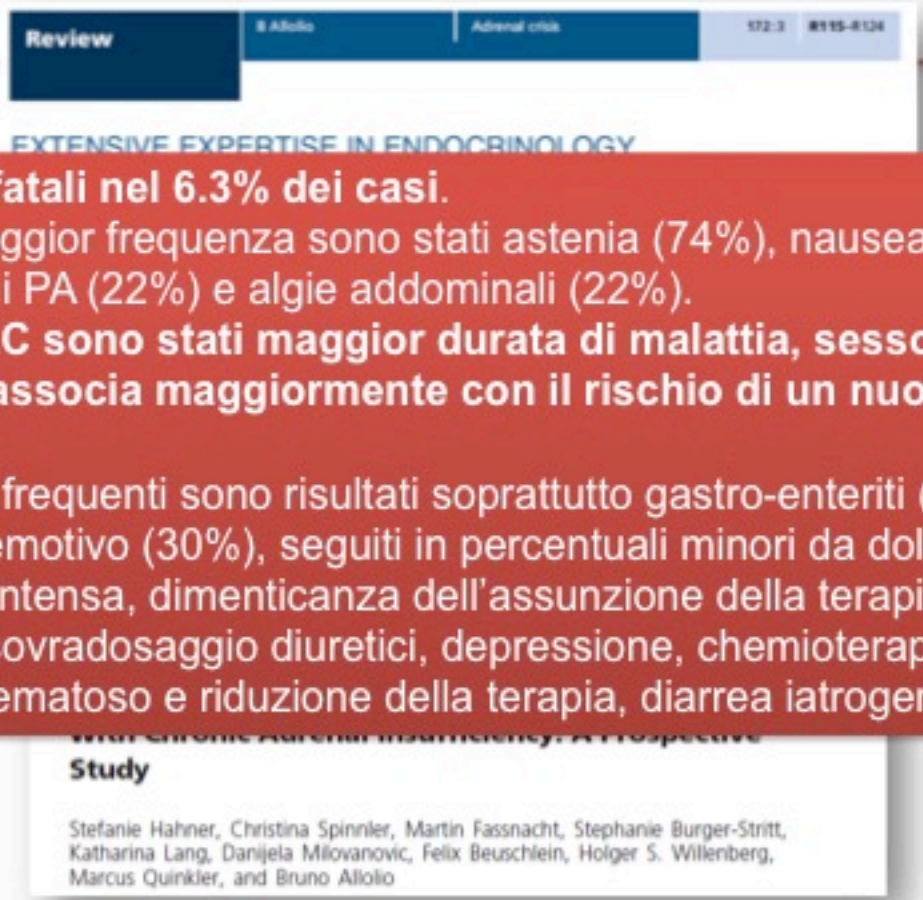
LA TERAPIA

Goal: mirror the normal physiology state

Hahner and Allolio, *Best Pract Clin Endocrinol Metab 2009; 23:167-179*

- Therapeutic options
  - Hydrocortisone
  - Hydrocortisone modified release
  - Cortisone acetate
  - Prednisone
  - Dexamethasone
- Treatment regimens
  - Fixed dose
  - Weight or m^2 related dose
  - Twice or thrice daily dose


Immune system
Sleep
Cognitive functions
Muscle metabolism
Energy
metabolism
Cortisol
Body composition
Bone
metabolism
Cardiovascular
system


Review

B Allolio

Adrenal crisis

172:3

R115–R124

EXTENSIVE EXPERTISE IN ENDOCRINOLOGY

Study

Stefanie Hahner, Christina Spinnler, Martin Fassnacht, Stephanie Burger-Stritt, Katharina Lang, Danijela Milovanovic, Felix Beuschlein, Holger S. Willenberg, Marcus Quinkler, and Bruno Allolio

8.3/100 pazienti-anno, fatali nel 6.3% dei casi.
I sintomi riportati con maggior frequenza sono stati astenia (74%), nausea (57%), vomito (52%), diarrea (45%), alterazioni PA (22%) e algie addominali (22%).
I fattori di rischio per AC sono stati maggior durata di malattia, sesso femminile e PAI.
Una precedente AC si associa maggiormente con il rischio di un nuovo episodio durante il *follow-up* (OR 2.9).
I **fattori precipitanti** più frequenti sono risultati soprattutto gastro-enteriti (34%), altre malattie infettive (32%) e *stress* emotivo (30%), seguiti in percentuali minori da dolore intenso, intervento chirurgico, attività fisica intensa, dimenticanza dell'assunzione della terapia, intossicazione da alcool, disidratazione o sovradosaggio diuretici, depressione, chemioterapia, puntura d'insetto, gravidanza con stato edematoso e riduzione della terapia, diarrea iatrogena.

Cortone Acetato

PROS	CONS
Cortisone acetate is available in Italy. Compared with HC, it shows a lower serum cortisol peak and delayed clearances of cortisol (2 daily doses; possible advantage)	Cortisone acetate requires activation to cortisol by hepatic 11betaHSD1, which contributes to a higher pharmacokinetic variability compared to HC. This conversion could be impaired in: • patients with congenital Cortisone Reductase Deficiency • patients treated with rhGH (GH may inhibit 11betaHSD1 expression) • patients with advanced liver disease.

Idrocortisone

Pros

- Hydrocortisone, i.e cortisol, do not require hepatic activation.
- HC shows a higher serum cortisol peak, followed by a rapid decline (< 3 mcg/dl 5-7 h after ingestion).
- Advantages of HC include the potential for fine dose adjustment with smaller fractionated doses (2-3 daily doses).
  - risk of over - replacement (?)

Cons

- It is not available in Italy.
- Patient compliance with thrice-daily dosing is far from absolute for many patients; possible increased risk of adrenal crisis, especially for older patients

ACTH deficiency: nothing to declare?

In addition, the mean 6-sample of cortisol day curves as well as the AUC were comparable with those during the low and the high daily dose, confirming the possibility of an adequate substitutive treatment with a lower and more physiological dose; this is particularly true in those patients, in whom only a partial hypoadrenalism of central origin occurs.

Barbetta et al. JEI 2005

Dosi più basse e aggiustamenti in funzione delle altre terapie ormonali concomitanti

…educed if there is

…al response to a
…ose of
…eplacement but
… traumatic stress

…rossman, JCEM 2010

Patients with secondary adrenal insufficiency may be taking other medication that can influence cortisol clearance, including growth hormone and oestrogens.
For patients on growth hormone there may be a requirement to increase the dose of hydrocortisone and concentrations of cortisol may be up to 20% lower after hydrocortisone when on growth hormone

Debono, Clin Endo 2012

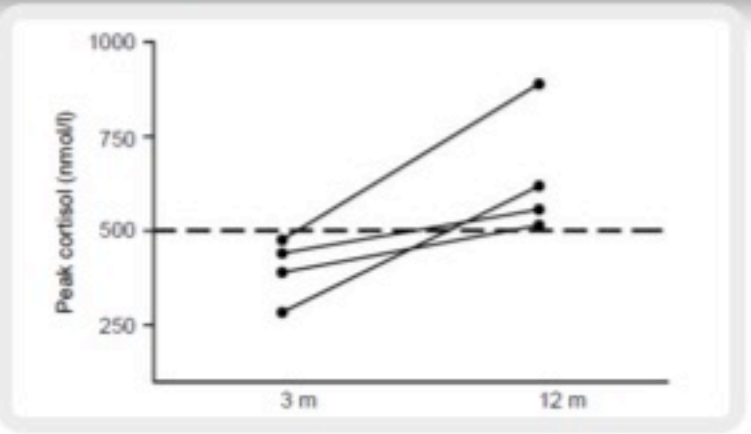
Per sempre?

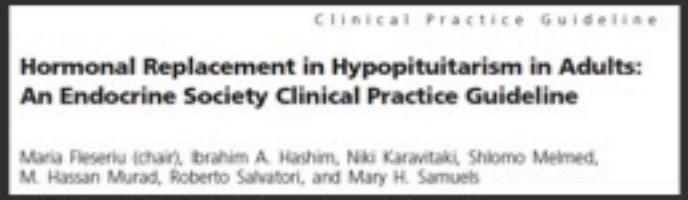
European Journal of Endocrinology (2010) 162 853–859 ISSN 0804-4643

CLINICAL STUDY

Recovery of pituitary function in the late-postoperative phase after pituitary surgery: results of dynamic testing in patients with pituitary disease by insulin tolerance test 3 and 12 months after surgery

C Berg, T Meinel, H Lahner, K Mann and S Petersenn




Clinical Practice Guideline

Hormonal Replacement in Hypopituitarism in Adults: An Endocrine Society Clinical Practice Guideline

Maria Fleseriu (chair), Ibrahim A. Hashim, Niki Karavitaki, Shlomo Melmed, M. Hassan Murad, Roberto Salvatori, and Mary H. Samuels

Clinicians also frequently prescribe single daily HC doses in patients with central AI

- We recommend using HC, usually 15–20 mg total daily dose in single or divided doses. Patients using divided doses should take the highest dose in the morning at awakening and the second in the afternoon (two-dose regimen) or the second and third at lunch and late afternoon, respectively (three-dose regimen). (1⊗⊗⊗○)
- We suggest using longer-acting GCs in selected cases (eg, nonavailability, poor compliance, convenience). (2⊗○○○)
- We recommend that clinicians teach all patients with AI regarding stress-dose and emergency GC administration and instruct them to obtain an emergency card/bracelet/ necklace regarding AI and an emergency kit containing injectable high-dose GC. (1⊗⊗⊗○)
- We recommend against using fludrocortisone in patients with secondary AI. (1⊗⊗⊗○)

Differenti regimi: pochi studi nel SAI

The HC 10 mg AM /5 mg PM regimen showed improved physical QOL, but overall QOL did not differ between regimens and remained lower than in healthy controls.

HC doses above 30 mg/d were associated with adverse health status by validated self-assessment questionnaires.

Three-times daily intake of HC was not superior to two-times-daily intake.

In 2737 adult hypopituitary patients, those receiving the equivalent of 10 mg HC had the best QOL, and those receiving 25 mg HC had the poorest QOL. These effects could be due to supraphysiological GC exposure, but it is possible that clinicians may have increased the GC doses to address unexplained QOL deficits.

Improved Cortisol Exposure-Time Profile and Outcome in Patients with Adrenal Insufficiency: A Prospective Randomized Trial of a Novel Hydrocortisone Dual-Release Formulation

Johannsson et al, JCEM 2012

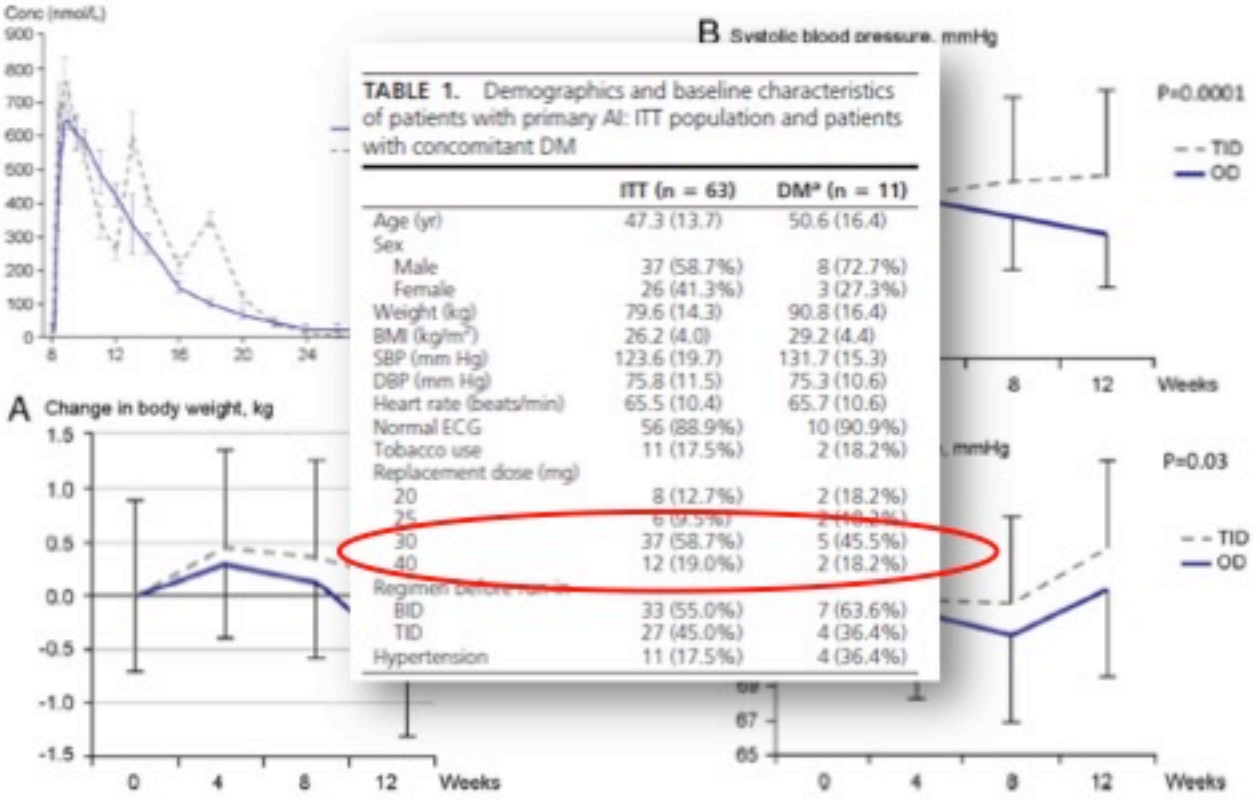


TABLE 1. Demographics and baseline characteristics of patients with primary AI: ITT population and patients with concomitant DM

	ITT (n = 63)	DM[a] (n = 11)
Age (yr)	47.3 (13.7)	50.6 (16.4)
Sex		
Male	37 (58.7%)	8 (72.7%)
Female	26 (41.3%)	3 (27.3%)
Weight (kg)	79.6 (14.3)	90.8 (16.4)
BMI (kg/m^2)	26.2 (4.0)	29.2 (4.4)
SBP (mm Hg)	123.6 (19.7)	131.7 (15.3)
DBP (mm Hg)	75.8 (11.5)	75.3 (10.6)
Heart rate (beats/min)	65.5 (10.4)	65.7 (10.6)
Normal ECG	56 (88.9%)	10 (90.9%)
Tobacco use	11 (17.5%)	2 (18.2%)
Replacement dose (mg)		
20	8 (12.7%)	2 (18.2%)
25	6 (9.5%)	2 (18.2%)
30	37 (58.7%)	5 (45.5%)
40	12 (19.0%)	2 (18.2%)
Regimen before [illegible]		
BID	33 (55.0%)	7 (63.6%)
TID	27 (45.0%)	4 (36.4%)
Hypertension	11 (17.5%)	4 (36.4%)

Improvement of anthropometric and metabolic parameters, and quality of life following treatment with dual-release hydrocortisone in patients with Addison's disease

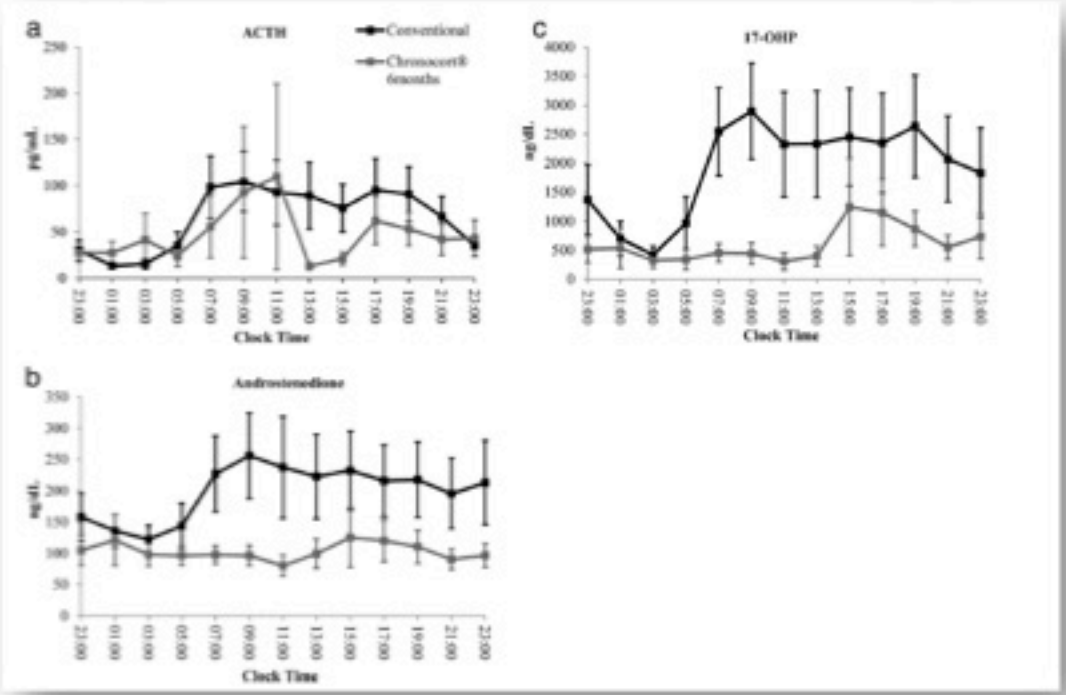
Roberta Giordano[1,2] · Federica Guaraldi[2] · Elisa Marinazzo[2] · Federica Fumarola[2] · Alessia Rampino[1] · Rita Berardelli[4] · Ioannis Karamouzis[2] · Manuela Lucchiari[3] · Tilde Manetta[3] · Giulio Mengozzi[3] · Emanuela Arvat[4] · Ezio Ghigo[2]

Modified-release hydrocortisone decreases BMI and HbA1c in patients with primary and secondary adrenal insufficiency

Outcome	Baseline		Follow-up		Estimated change per 30 days[a]			
	No. of patients	Observed mean ± S.E.M.	No. of patients	Observed mean ± S.E.M.	β ± S.E.M.	P change	Adjusted β ± S.E.M.[b]	Adjusted P change
AddiQoL								
Modified release HC	30	83.8 ± 1.81	30	84.9 ± 1.95	0.157 ± 0.167	0.348	0.081 ± 0.167	0.629
Conventional HC	20	84.0 ± 2.11	20	80.9 ± 2.50	−0.299 ± 0.130	0.021	−0.305 ± 0.127	0.016
interaction[c]					0.031		0.066	
Fatigue								
Modified release HC	30	22.4 ± 0.68	30	22.6 ± 0.81	0.047 ± 0.064	0.464	0.017 ± 0.064	0.793
Conventional HC	20	21.1 ± 0.66	20	19.9 ± 0.85	−0.108 ± 0.050	0.030	−0.110 ± 0.049	0.024
interaction[c]					0.057		0.116	
BMI								
Modified release HC	30	26.0 ± 0.75	30	25.6 ± 0.71	−0.057 ± 0.019	0.003	−0.056 ± 0.020[d]	0.006
Conventional HC	20	25.7 ± 1.14	20	25.8 ± 1.08	0.002 ± 0.015	0.887	0.000 ± 0.015[d]	0.985
interaction[c]					0.015		0.029[d]	
HbA1c								
Modified release HC	27	6.04 ± 0.29	28	5.86 ± 0.28	−0.020 ± 0.008	0.014	−0.023 ± 0.008[e]	0.005
Conventional HC	20	5.63 ± 0.13	18	5.72 ± 0.15	−0.0002 ± 0.006	0.975	0.001 ± 0.006[e]	0.807
interaction[c]					0.049		0.017e	
Cholesterol								
Modified release HC	30	213.8 ± 7.97	29	200.1 ± 7.57	−1.835 ± 0.760	0.016	−1.655 ± 0.787	0.036
Conventional HC	19	221.8 ± 10.8	19	210.9 ± 13.1	−0.586 ± 0.604	0.332	−0.605 ± 0.608	0.320
interaction[c]					0.198		0.294	

A Phase 2 Study of Chronocort, a Modified-Release Formulation of Hydrocortisone, in the Treatment of Adults With Classic Congenital Adrenal Hyperplasia

Ashwini Mallappa, Ninet Sinaii, Parag Kumar, Martin J. Whitaker, Lori-Ann Daley, Dena Digweed, David J. A. Eckland, Carol Van Ryzin, Lynnette K. Nieman, Wiebke Arlt, Richard J. Ross, and Deborah P. Merke



Interazione fra le terapie sostitutive

ITALIAN CHAPTER

GH

- Because GH suppresses the conversion of cortisone to cortisol, patients receiving GC replacement may require higher doses once GH is initiated, and those with low adrenal reserve may be rendered hypoadrenal by the GH therapy

Thyroid

- Data suggest that AI should be conclusively excluded before initiating L-T4 therapy for CH. This is because thyroid hormone accelerates endogenous cortisol clearance and could unmask insufficient cortisol production and precipitate AC.

Estrogen

- Oral estrogen therapy increases circulating CBG (through a hepatic first-pass effect), leading to increased total cortisol levels; this does not occur with transdermal estrogen therapy

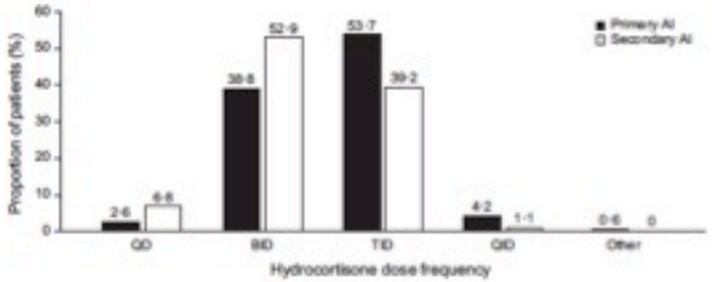
Clinical Endocrinology (2017) 86, 340–346 doi: 10.1111/cen.13267

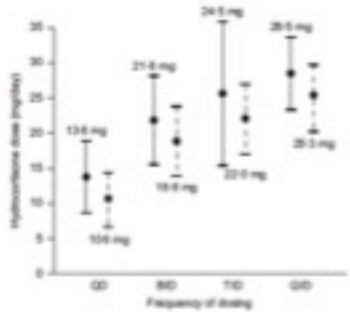
ORIGINAL ARTICLE

Management of glucocorticoid replacement in adrenal insufficiency shows notable heterogeneity – data from the EU-AIR

Robert D. Murray*, Bertil Ekman†‡, Sharif Uddin§, Claudio Marelli¶, Marcus Quinkler**, Pierre M.J. Zelissen†† and on behalf of the EU-AIR Investigators

	Primary AI	Secondary AI	Overall
Patient numbers, n	364	801	1166
Female, n (%)	237 (65·1)	374 (46·7)	612 (52·5)
Age, years, mean ± SD	52·0 ± 15·8	55·2 ± 16·0	54·3 ± 16·0
Disease duration, years, n (mean ± SD)	364 (17·6 ± 12·6)	800 (13·4 ± 10·9)	1166 (14·1 ± 11·6)
BMI, kg/m², n (mean ± SD)	321 (26·2 ± 4·6)	695 (28·6 ± 5·1)	1016 (27·9 ± 5·2)
Diabetes, n (%)	51 (14·0)	94 (11·7)	145 (12·4)
Hypertension, n (%)	92 (25·3)	263 (32·8)	355 (30·4)





ITALIAN CHAPTER

Un’unica dose tante possibilità….

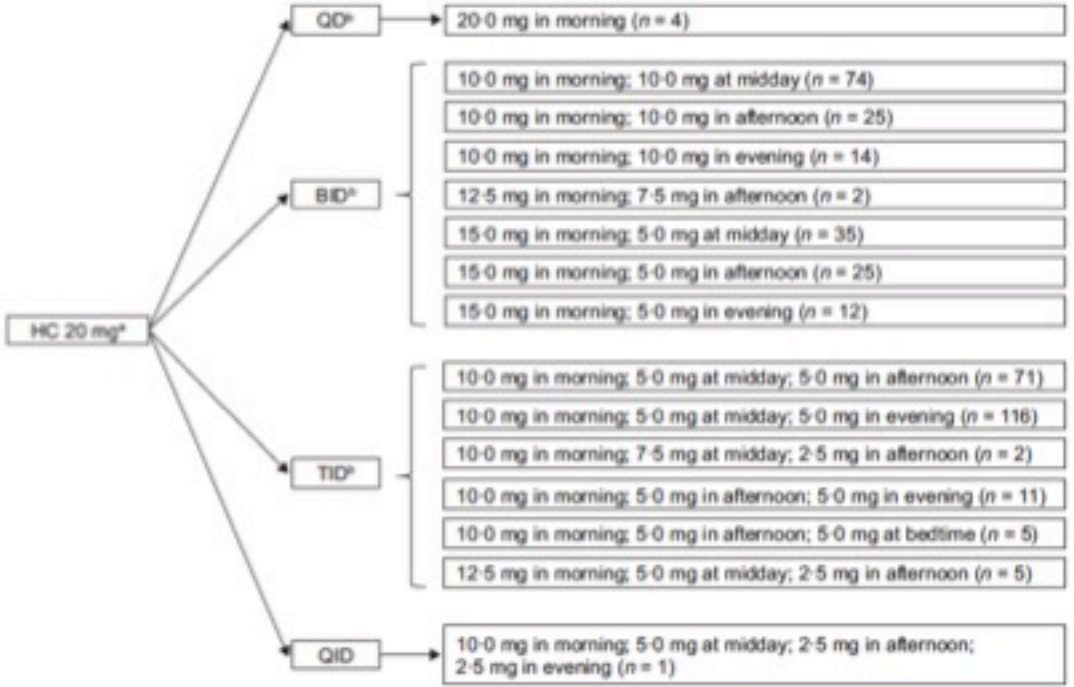


Table 6 *Treatment during surgery, dental procedures, delivery and invasive procedures*[a]

Procedure	Preoperative needs	Postoperative needs
Major surgery with long recovery time	100 mg hydrocortisone im just before anaesthesia	Continue 100 mg hydrocortisone im every 6 h until able to eat and drink. Then double oral dose for 48+ h, then taper to normal dose
Major surgery with rapid recovery	100 mg hydrocortisone im just before anaesthesia	Continue 100 mg hydrocortisone im every 6 h for 24–48 h. Then double oral dose for 24–48 h, then taper to normal dose
Labour and vaginal birth	100 mg hydrocortisone im just at onset of labour	Double oral dose for 24–48 h after delivery, then taper to normal dose
Minor surgery and major dental surgery	100 mg hydrocortisone i/m just before anaesthesia	Double oral dose for 24 h, then return to normal dose
Invasive bowel procedures requiring laxatives	Hospital admission overnight with 100 mg hydrocortisone im and fluid., repeat dose before start of procedure	Double oral dose for 24 h, then return to normal dose
Other invasive procedures	100 mg hydrocortisone im just before start of procedure	Double oral dose for 24 h, then return to normal dose
Dental procedure	Extra morning dose 1 h prior to surgery	Double oral dose for 24 h, then return to normal dose
Minor procedure	Usually not required	Extra dose (e.g. 20 mg hydrocortisone) if symptoms

[a]Material reproduced from UK Addison's disease self-help group, www.addisons.org.uk.

Table 7 *Treatment of acute adrenal insufficiency*

Treatment	Dose/procedure
Hydrocortisone	100 mg bolus given immediately followed by 100–300 mg day^{-1} as continuous infusion or frequent intravenous or intramuscular boluses every 6 h
Intravenous substitution of fluids	3–4 L isotonic saline or 5 per cent dextrose in isotonic saline with an initial infusion rate of approximately 1 L h^{-1}; frequent hemodynamic monitoring and measurement of serum electrolytes to avoid fluid overload
Depending on the severity of the intercurrent illness	Admission to the intensive care or high-dependency unit; prophylaxis of gastric stress ulcer; low-dose heparin; antibiotic treatment

Fig. 2 *The Swedish duplex steroid card for adults with English and Swedish text. A version for children also exists. Equivalent cards are also used in Norway.*

Caso Clinico 2

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Paziente di sesso maschile, età 55 anni

ANAMNESI

- **Ipotiroidismo in tiroidite autoimmune (diagnosi oltre 20 anni fa), in trattamento sostitutivo con Levotiroxina-sodica 75 mcg/ die.**
- **Obesità e dislipidemia in trattamento nutrizionale da oltre 20 anni.**

ANAMNESI

- All'età di 45 anni incidente stradale (trauma cranico, accertamenti neuroradiologici negativi).
- Nell'anno successivo sviluppa una sintomatologia caratterizzata da: astenia, turbe dell'umore e del sonno, vago malessere, ridotta potenza sessuale.

ANAMNESI

Accertamenti in tal data:

- **Testosterone = 0,86 ng/ml ; FSH=0,2 mUI/ml; LH=0,1 mUI/ml;**
- **Prolattina = 7,0 ng/ml;**
- **ACTH = 6 pg/ml ; cortisolo = 2,5 mcg/dl;**
- **TSH = 0,5 mcUI/ml; FT4 = 0,98 ng/dl;**
- **GH = 0,5 ng/ml;**
- **Creatinina = 1,01 mg/dl ; Na = 132 mEq/L ; K = 4,0**
  Glicemia = 78 mg/dl ; calcemia = 8,5 mg/dl;
- **RM ipotalamo ipofisi con mdc: sella vuota**

DIAGNOSI:

IPOCORTICOSURRENALISMO SECONDARI

IPOGONADISMO SECONDARIO

Avreste effettuato altre indagini o approfondito gli accertamenti?

1.0 Diagnosis of hypopituitarism

Central adrenal insufficiency

1.1 We suggest measuring serum cortisol levels at 8–9 AM as the first-line test for diagnosing central adrenal insufficiency (AI). (2|⊕◯◯◯)

1.2 We recommend against using a random cortisol level to diagnose AI. (1|⊕⊕◯◯)

1.3 We suggest that a cortisol level <3 μg/dL is indicative of AI and a cortisol level >15 μg/dL likely excludes an AI diagnosis. (2|⊕◯◯◯)

MALATTIE IPOFISARIE
Lesioni espansive: Adenomi; Cisti; Altri tumori benigni
Neurochirurgia dell'ipofisi
Radiazioni
Lesioni infiltrative: Ipofisiti; Emocromatosi
Sindrome di Sheehan
Apoplessia ipofisaria
Malattie Genetiche: pit-1 mutazione

MALATTIE IPOTALAMICHE
Lesioni espansive benigne e maligne: Craniofaringioma; Metastasi (polmone; stomaco etc)
Processi infiltrativi: sarcoidosi ; Istiocitosi a cellule di Langerans
Radiazioni: ETP SNC / Naso-faringe
Traumi (fratture della base)
Infezioni: meningite TBC

TRAUMA CRANICO

DEFICIT ACTH

11 %

Incidence and prevalence of hypopituitarism are estimated to be 4.2 per 100,000 per year and 45.5 per 100,000, respectively. Although the clinical symptoms of this disorder are usually unspecific, it can cause life-threatening events and lead to increased mortality. Current research has refined the diagnosis of hypopituitarism. Identification of growth hormone and corticotropin deficiency generally requires a stimulation test, whereas other deficiencies can be detected by basal hormones in combination with clinical judgment. Newly developed formulations of replacement hormones are convenient and physiological. **Work has shown that many patients with brain damage--such as traumatic brain injury or aneurysmal subarachnoid haemorrhage--are at high risk of (sometimes unrecognised) hypopituitarism.** Thus, a much increased true prevalence of this disorder needs to be assumed. As a result, **hypopituitarism is not a rare disease and should be recognised by the general practitioner.**

	n	Any degree of hypopituitarism	Multiple deficiencies	GH	LH/FSH	ACTH	TSH	Remarks
Kelly et al, 2000[9]	22	8	3	4	4	3	1	
Lieberman et al, 2001[4]	70	48	12	7	2	12	15	32 patients with low morning cortisol; only 5 patients with cortisol <500 nmol/l after ACTH stimulation
Bondanelli et al, 2004[5]	60	27	6	4	7	0	5	No stimulation test for ACTH
Agha et al, 2004[10]	103	26	6	11	12	13	1	
Popovic et al, 2004[6]	67	23	7	10	6	5	3	
Aimaretti et al, 2005[11]	70	16	7	14	8	4	5	No stimulation test for ACTH
Leal-Cerro et al, 2005[7]	370	42	14	6	29	11	10	Endocrine testing only if clinical suspicion of hypopituitarism (n=59)
Schneider et al, 2005[8]	70	25	3	7	14	6	2	
Tanriverdi et al, 2006[12]	52	26	5	17	4	10	3	
Heinmann et al, 2006[13]	76	18	5	6	13	2	2	
Total (%)	560 (100)	262 (35)	69 (9)	86 (11)	99 (13)	64 (13)	47 (6)	

LH=luteinising hormone. FSH=follicle-stimulating hormone. GH=growth hormone. ACTH=adrenocorticotropic hormone. TSH=thyrotropic hormone.

Table 1: Hypopituitarism in the chronic phase after traumatic brain injury

Lancet. 2007

Hypopituitarism

Schneider HJ [1], Aimaretti G. Kreitschmann-Andermahr I. Stalla GK Ghigo E

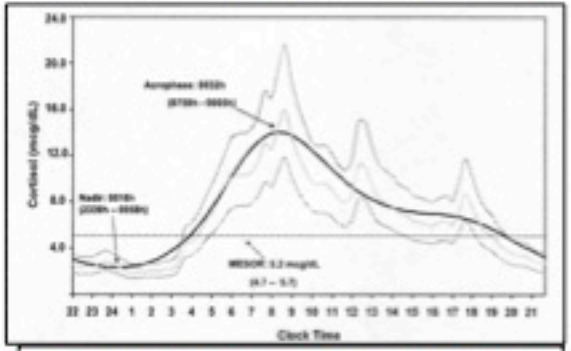
TERAPIA ALLA DIAGNOSI

- Levotiroxina sodica 75 mcg: una cpr al dì
- Cortisone acetato 25 mg: ½ cpr dopo colazione; ½ cpr ore 16.00
- Testosterone enantato 250 mg: una fiala im ogni 4 settimane

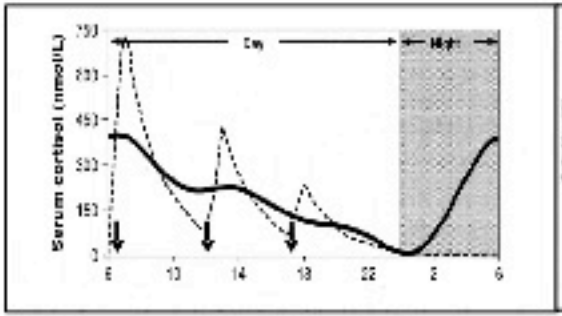
AVRESTE PROPOSTO MODIFICHE DELLA POSOLOGIA O FORMULAZIONI DIVERSE?

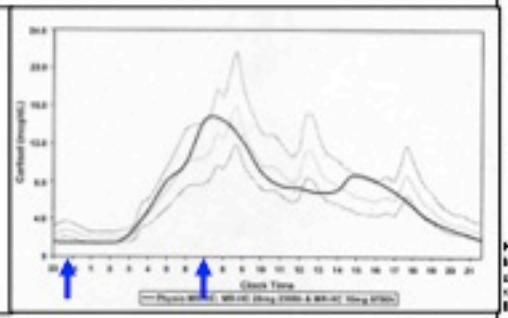
QUALI POSSIBILI INTERFERENZE FARMACOLOGICHE?

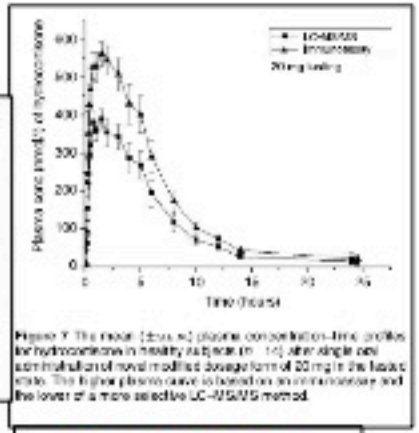
TERAPIE DELL'INSUFFICIENZA CORTICOSURRENALICA



Ritmo circadiano del cortisolo







Terapia Tradizionale
2 o 3 dosi di Idrocortisone
o di cortone

Chronocort
2 dosi

PLENADREN
1 dose

Recommended therapeutic approach to secondary adrenal insufficiency

Glucocorticoid replacement

Immediate-release hydrocortisone dosing:

- Start on 15–20 mg hydrocortisone per 24 hours
- Administer in 2 or 3 divided doses
- Administer ⅔ or ⅓ the dose, respectively, immediately after waking

Once-daily modified-release hydrocortisone dosing:

- Dose based on clinical response, 20 mg/day
- Administer once daily in the morning

Consider:

- 10 mg or stress dose cover only if borderline fail in ACTH

Mineralocorticoid replacement

- Not required

Adrenal androgen replacement

Consider in:

- Patients with impaired well-being and mood despite optimised glucocorticoid replacement therapy
- Women with symptoms and signs of androgen deficiency

Dosing:

- DHEA 25–50 mg as a single morning dose
- In women also consider transdermal testosterone

ANAMNESI PATOLOGICA PROSSIMA

GIORNO 1

- consulto con MMG per faringodinia, nausea vaga epigastralgia, febbrico
- EO: erit ndibolare bilateral trattabile vaga dol mmHg, fc 82/min
- Terapia: azitromicina 500 mg: 1 c al dì, betametasone 1 mg: 1 c al dì (per 3 giorni)
- Richiesto RX torace in urgenza differita

IN CORSO DI EVENTO ACUTO "STRESS"
COME COMPORTARSI?

	Primary AI (181 cases) % of cases	Secondary AI (110 cases) % of cases
Gastrointestinal infection	**32.6**	**21.8**
Other infectious disease/fever	**24.3**	**17.3**
Surgery	7.2	15.5
Unknown	6.6	12.7
Strenuous physical activity	7.7	7.3
Cessation of glucocorticoid substitution by patient	5.0	6.4
Neglected glucocorticoid intake	5.0	3.6
Psychic distress	3.3	3.6
Accident	2.8	2.7
Cessation of glucocorticoid substitution by attending physician	1.1	3.6
Other reasons*	4.4	5.4

Tabella 1
Linee guida per la supplementazione corticosurrenalica in condizioni di *stress*

	Stress medico o chirurgico	Dosaggio corticosteroidi
Minimo	Pratiche dentarie routinarie Biopsia tiroidea Infezioni non febbrili vie respiratorie superiori	Abituale (+ 20 mg idrocortisone per *os* se sintomi)
Minore	Estrazioni dentarie Ernia inguinale Colonscopia Stati febbrili Infezioni urinarie non complicate Celluliti non complicate Malattie virali Bronchiti	Raddoppiare o triplicare la dose sostitutiva il giorno della procedura e/o mantenerla fino a persistenza dei sintomi
Moderato	Colecistectomia Emicolectomia Malattie febbrili severe Polmoniti Gastroenteriti Pielonefriti Parto naturale o cesareo	100 mg idrocortisone im o ev nel giorno della procedura o fino a persistenza dei sintomi
Severo	Chirurgia toracica maggiore Gastro-resezione Resezione epatica Pancreatiti Trauma maggiore Infarto del miocardio	100 mg idrocortisone bolo ev seguito da 50 mg ev o im ogni 6 ore il giorno della procedura o fino a stabilizzazione clinica
Critico	Sepsi inducente ipotensione o *shock*	100 mg idrocortisone bolo ev seguito da 50 mg ev ogni 6-8 ore o infusione continua 50 µg/kg/h; proseguire fino a stabilizzazione clinica e quindi riprendere la dose abituale per os

ANAMNESI PATOLOGICA PROSSIMA

GIORNO 2

- RX TORACE: strie di atelettasia basale destra, obliterazione seno costo-frenico destro; non addensamenti pleuro-parenchimali in atto.
- EO: compromissione stato generale, dolore epigastrico irradiato all'ipocondrio destro, Murphy positivo, PA 96/50 mmHg; fc 88/min; T 38.5° C.
- Il paziente viene inviato in Pronto Soccorso.

ACCERTAMENTI IN PRONTO SOCCORSO

- GB: 18.200, Hb 10.8; PCR20 mg/dl; GOT = 60 UI/L GPT = 72 UI/L, gammaGT = 250 UI/L, bilirubina tot = 3.2 mg/dl, creatinina = 1.2 mg/dl, Na = 130 mEq/L; K = 4,2 mEq/L
- ECO ADDOME: colecisti distesa contenente calcoli e fango biliare, parete ispessita, edema pericolecistico.

DIAGNOSI

colecistite acuta in litiasi biliare

TERAPIA IN PRONTO SOC

Corretta la gestione della crisi surrenalica?

- **Idrocortisone 100 mg e.v.**
- **Soluzione salina 500 cc in due ore**
- **Ceftriaxone 1gr e.v.**
- **Paziente inviato reparto chirurgico**

4.0 Management and prevention of adrenal crisis in patients with PAI

4.1 We recommend that patients with suspected adrenal crisis should be treated with an immediate parenteral injection of 100 mg (50 mg/m^2 for children) hydrocortisone, followed by appropriate fluid resuscitation and 200 mg (50–100 mg/m^2 for children) of hydrocortisone/24 hours (via continuous iv therapy or 6 hourly injection); age- and body surface-appropriate dosing is required in children (see Table 3). (1|⊕⊕⊕○)

4.2 If hydrocortisone is unavailable, we suggest prednisolone as an alternative. Dexamethasone is the least-preferred alternative and should only be given if no other glucocorticoid is available. (2|⊕⊕○○)

4.3 For the prevention of adrenal crisis, we suggest adjusting glucocorticoid dose according to severity of illness or magnitude of the stressor. (2|⊕⊕○○)

Table 6 *Treatment during surgery, dental procedures, delivery and invasive procedures*[a]

Procedure	Preoperative needs	Postoperative needs
Major surgery with long recovery time	100 mg hydrocortisone im just before anaesthesia	Continue 100 mg hydrocortisone im every 6 h until able to eat and drink. Then double oral dose for 48+ h, then taper to normal dose
Major surgery with rapid recovery	100 mg hydrocortisone im just before anaesthesia	Continue 100 mg hydrocortisone im every 6 h for 24–48 h. Then double oral dose for 24–48 h, then taper to normal dose
Labour and vaginal birth	100 mg hydrocortisone im just at onset of labour	Double oral dose for 24–48 h after delivery, then taper to normal dose
Minor surgery and major dental surgery	100 mg hydrocortisone i/m just before anaesthesia	Double oral dose for 24 h, then return to normal dose
Invasive bowel procedures requiring laxatives	Hospital admission overnight with 100 mg hydrocortisone im and fluid, repeat dose before start of procedure	Double oral dose for 24 h, then return to normal dose
Other invasive procedures	100 mg hydrocortisone im just before start of procedure	Double oral dose for 24 h, then return to normal dose
Dental procedure	Extra morning dose 1 h prior to surgery	Double oral dose for 24 h, then return to normal dose
Minor procedure	Usually not required	Extra dose (e.g. 20 mg hydrocortisone) if symptoms