V Corso Aggiornamento Ame
in Endocrinologia Clinica

AGRIGENTO
Museo Archeologico

20/22 MARZO
2014

AGGIORNAMENTI su PATOLOGIA SURRENALICA

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Di cosa parleremo ?

- Ipercortisolismo
  - Approccio clinico – screening di laboratorio
  - Cenni di terapia farmacologica
- Ipertensione resistente
  - Approccio clinico e screening di laboratorio nell'Iperaldosteronismo Primitivo

It Is Important to Diagnose Cushing's Disease Early Due to Excess of Mortality and Morbidity

- The diagnosis of Cushing's disease first requires the confirmation of chronic endogenous hypercortisolism (ie, Cushing's syndrome)
- Early diagnosis of Cushing's syndrome is crucial, as the natural history of the condition is marked by a significant excess of mortality and morbidity
  - Cardiovascular diseases
  - Severe infections
  - Osteoporosis and bone fractures
  - Psychiatric disorders

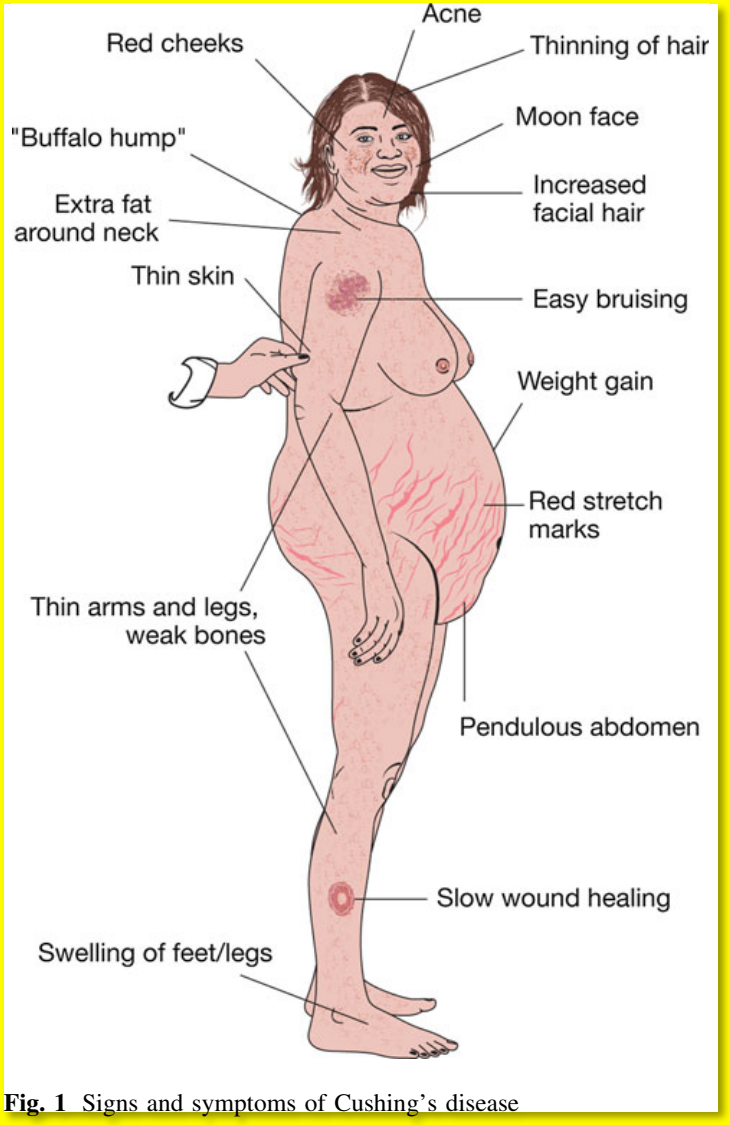


Fig. 1 Signs and symptoms of Cushing's disease

- A chi proporre accertamenti ?
- Quali ?
- Cenni di Terapia Farmacologica

Caso clinico

Daniela, di anni 48

AP: familiarità per ICTUS CEREBRI ed IPERTENSIONE ARTERIOSA;
IPERTESA da 8 anni. IPERCOLESTEROLEMIA. DIABETE tipo 2. OBESA 1 grado.

Terapia: ACEI + DIURETICO; IPOCOLESTEROLEMIZZANTE; ANTIAGGREGANTE; DIETA + METFORMINA

Negli ultimi 10 anni aumenta di peso con accentuazione negli ultimi due anni; adotta una dieta ipocalorica che riesce a farLe perdere significativamente peso

Nell'ultimo anno per controllare efficacemente la PA associa all'ACE Inibitore anche il diuretico.

ECOCOLORDOPPLER TSA (2013): note diffuse di ateromasia di parete;
bilateralmente, al bulbo e all'origine della C.I., placca realizzante stenosi del 30% a destra e del 40% a sinistra

Caso clinico

Es. Obiettivo:

- PA 130/85 con fc 68 bpm, regolare;
- peso 70,5 Kg, altezza 150 cm, BMI 31,3 Kg/m^2
- Facies «piena», non striae rubrae, non gibbosità, non ecchimosi, non segni di iperandrogenismo.

In una paziente con queste caratteristiche avreste avviato uno screening per Cushing ?

Screening negli obesi?

SCREENING FOR CUSHING'S SYNDROME IN OBESE PATIENTS

Ozay Tiryakioglu, Serdal Ugurlu, Serap Yalin, Sibel Yirmibescik, Erkan Caglar, Demet Ozgil Yetkin, Pinar Kadioglu

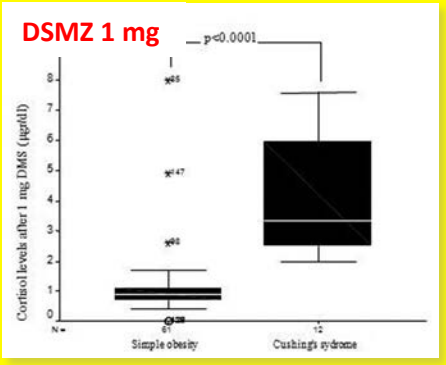
Division of Endocrinology and Metabolism, Department of Internal Medicine, Cerrahpasa Medical Faculty - Sivas, Turkey.

Table 2 - Laboratory findings in the study patients

	Simple obesity	Cushing's syndrome	*p*
ACTH (pg/ml)	25.7 *[15-51]*	35 *[13.5-94.5]*	0.43
Cortisol (µg/dL)	10.2 *[7.8-14.8]*	9.4 *[8.1-13.5]*	0.88
Glucose (mg/dL)	99 *[91-113]*	100 *[93.5-114]*	0.91
Insulin (mU/ml)	14.7 *[7.4-24.2]*	18.9 *[14.9-28.5]*	0.07
f T4 (ng/dL)	1.2 *[1.07-1.4]*	1.1 *[1.04-1.63]*	0.56
TSH (mIU/L)	1.64 *[0.9-2.8]*	1.78 *[1.6-4.2]*	0.25
Cholesterol (mg/dL)	203 *[172-249]*	238.5 *[178.-264]*	0.24
LDL-c (mg/dL)	129 *[97-159]*	168 *[122-168]*	0.15
HDL-c (mg/dL)	44 *[37.5-50.5]*	46 *[29-66]*	0.72
VLDL-c (mg/dL)	24 *[17-33]*	38 *[16.2-50]*	0.2
Triglyceride (mg/dL)	120 *[86-161]*	208 *[89.8-251]*	0.15
Urine cortisol (µg/24 h)	28 *[15-92.5]*	74 *[27-133]*	0.02
DMST cortisol (µg/dL)	0.88 *[0.7-1.15]*	3.35 *[2.5-6.5]*	< 0.0001
HOMA-R (mg/dl x mU/ml)	4.02 *[1.91-6.59]*	4.66 *[4.38-9.08]*	0.06

Values are medians and interquartile ranges.
DMST: 1-mg dexamethasone suppression test

All patients in our study had simple obesity; none of them had diabetes mellitus. Since the patients had simple obesity, careful examinations did not reveal hirsutism, buffalo hump, easy bruising, or any other manifestations suggestive of CS suggestive manifestations.



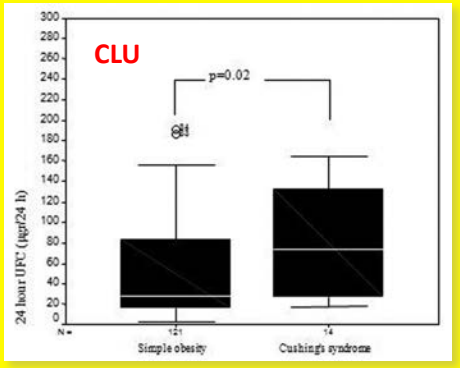


Table 3 - Etiologies of the 14 patients diagnosed with Cushing's syndrome

150 soggetti

	N	%
Pituitary adenoma	**9**	**64.28**
Surrenal cortex adenoma	**3**	**21.42**
Surrenal cortex carcinoma	**1**	**7.15**
Declined further evaluation	**1**	**7.15**

CLINICS 2010;65(1):9-13

CONCLUSION: A significant proportion (9.33%) of patients with simple obesity were found to have Cushing's syndrome. These findings argue that obese patients should be routinely screened for Cushing's syndrome.

Hindawi Publishing Corporation
ISRN Endocrinology
Volume 2013, Article ID 321063, 4 pages
http://dx.doi.org/10.1155/2013/321063

Clinical Study

Routine Screening for Cushing's Syndrome Is Not Required in Patients Presenting with Obesity

Serap Baydur Sahin,[1] Hacer Sezgin,[2] Teslime Ayaz,[3] Emine Uslu Gur,[3] and Kadir Ilkkilic[3]

N° Soggetti	354
Test DST 1 mg (> 1,8 mcg/dl)	7 (2%)
Test DST 2 mg in 2 gg (> 1,8 mcg/dl)	2 (0,6%)

Nei 2 soggetti:
-UFC nella norma
-ACTH < 5 pg/ml
-"elevated midnight Cortisol"

DIAGNOSI: Adenoma Surrenalico

In conclusion, the present data do not support widespread screening of obese patients for Cushing's syndrome. We suggest that examination for hypercortisolism should only be performed in obese patients with a cushingoid appearance and hypertension or glucose intolerance or dyslipidaemia.

Screening of Cushing's Syndrome in Outpatients with Type 2 Diabetes: Results of a Prospective Multicentric Study in Italy

Massimo Terzolo, Giuseppe Reimondo, Iacopo Chiodini, Roberto Castello, Roberta Giordano, Enrica Ciccarelli, Paolo Limone, Claudio Crivellaro, Irma Martinelli, Marcella Montini, Olga Disoteo, Bruno Ambrosi, Roberto Lanzi, Maura Arosio, Sanzio Senni, Antonio Balestrieri, Erica Solaroli, Bruno Madeo, Raffaella De Giovanni, Felice Strollo, Rodolfo Battista, Alessandro Scorsone, Vito A. Giagulli, Daniela Collura, Aldo Scillitani, Renato Cozzi, Marco Faustini-Fustini, Anna Pia, Roberta Rinaldi, Barbara Allasino, Giulia Peraga, Francesco Tassone, Piernicola Garofalo, Enrico Papini, and Giorgio Borretta*

In conclusion, the results of the present study do not support the application of a wide-scale screening of Cushing's syndrome in patients with type 2 diabetes, unless more efficient screening procedures will become available. The frequency of Cushing's syndrome in an unselected patient population was low compared with the number of false-positive results to make a routine screening strategy applicable in practice.

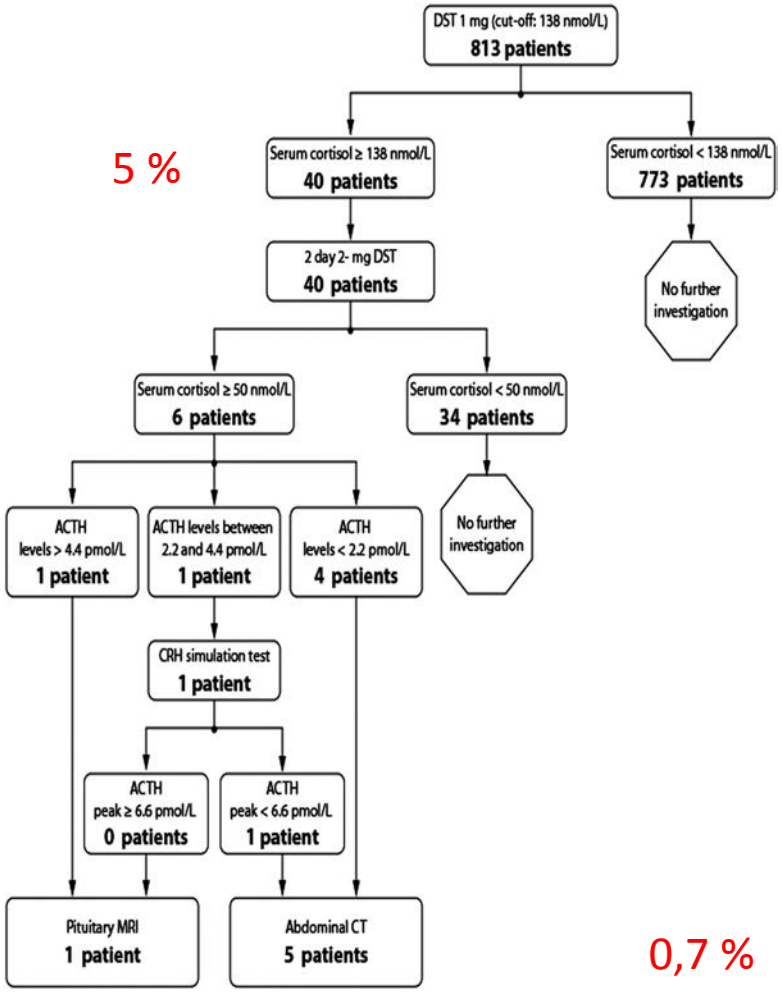


FIG. 1. Flow-chart of the study.

J Clin Endocrinol Metab, October 2012, 97(10):3467–3475

Long-Term Follow-Up in Adrenal Incidentalomas: An Italian Multicenter Study

Valentina Morelli, Giuseppe Reimondo, Roberta Giordano, Silvia Della Casa, Caterina Policola, Serena Palmieri, Antonio S. Salcuni, Alessia Dolci, Marco Mendola, Maura Arosio, Bruno Ambrosi, Alfredo Scillitani, Ezio Ghigo, Paolo Beck-Peccoz, Massimo Terzolo, and Iacopo Chiodini

Table 3. Occurrence of CVEs and Changes in Body Weight, Blood Pressure, Glycemic and LDL Cholesterol Control in Patients With and Without SH at the End of Follow-Up

	SH− Group	SH+ Group	*P*
n	167	39	
Duration of follow-up, mo	83.2 ± 33.6 (60–186)	79.4 ± 25.2 (60–178)	.826
New CVE	14 (8.4)	8 (20.5)	.040
New CVE in CVE− patients at baseline	11 (6.6)	4 (10.0)	.343
Increased body weight[a]	40 (24.0)	13 (33.3)	.229
Worsened blood pressure control[b]	52 (31.1)	18 (46.2)	.070
Worsened glycemic control[c]	39 (23.4)	12 (30.8)	.334
Worsened LDL[c]	20 (12.0)	7 (17.9)	.303

Data are expressed as mean ± SD (range) or absolute number of patients (percentage). CVE− indicates patients without previous CVEs.

[a] Body weight is considered improved or worsened in the presence of at least a 5% variation with respect to baseline (37).

[b] Blood pressure level was considered improved or worsened if it passed from one category to the other, in agreement with the guidelines of the European Societies of Hypertension and Cardiology (34).

[c] Fasting glucose and LDL-cholesterol levels were considered improved or worsened if they passed from one category to the other, in agreement with the Adult Treatment Panel III criteria (36).

J Clin Endocrinol Metab, March 2014, 99(3):827–834

In **conclusione**:

a. l'IS espone il paziente con AI al rischio di sviluppare nuovi ECV e di aumentata mortalità. Questi fattori sembrano associati ai livelli di cortisolemia dopo 1mg-DST;
b. i pazienti con un adenoma > 2.4 cm mostrano un rischio maggiore di sviluppare IS, per cui è necessario eseguire oltre al *follow-up* clinico, atto a valutare la comparsa di fattori di rischio cardiovascolare come DMT2 e ipertensione arteriosa, anche un *follow-up* biochimico di lunga durata.

The Diagnosis of Cushing's Syndrome:

An Endocrine Society Clinical Practice Guideline

3.2. We recommend testing for Cushing's syndrome in the following groups:

- Patients with unusual features for age (*e.g.* osteoporosis, hypertension) (Table 1) (1 | ⊕⊕◯◯)
- Patients with multiple and progressive features, particularly those who are more predictive of Cushing's syndrome (Table 1) (1 | ⊕⊕◯◯)
- Children with decreasing height percentile and increasing weight (1 | ⊕◯◯◯)
- Patients with adrenal incidentaloma compatible with adenoma (1 | ⊕◯◯◯).

Diabete tipo 2 in giovane età

3.3. We recommend against widespread testing for Cushing's syndrome in any other patient group (1 | ⊕◯◯◯).

The Diagnosis of Cushing's Syndrome:

An Endocrine Society Clinical Practice Guideline

TABLE 1. Overlapping conditions and clinical features of Cushing's syndrome[a]

Symptoms	Signs	Overlapping conditions
Features that best discriminate Cushing's syndrome; most do not have a high sensitivity		
	Easy bruising	
	Facial plethora	
	Proximal myopathy (or proximal muscle weakness)	
	Striae (especially if reddish purple and >1 cm wide)	
	In children, weight gain with decreasing growth velocity	
Cushing's syndrome features in the general population that are common and/or less discriminatory		
Depression	Dorsocervical fat pad ("buffalo hump")	Hypertension[b]
Fatigue	Facial fullness	Incidental adrenal mass
Weight gain	Obesity	Vertebral osteoporosis[b]
Back pain	Supraclavicular fullness	Polycystic ovary syndrome
Changes in appetite	Thin skin[b]	Type 2 diabetes[b]
Decreased concentration	Peripheral edema	Hypokalemia
Decreased libido	Acne	Kidney stones
Impaired memory (especially short term)	Hirsutism or female balding	Unusual infections
Insomnia	Poor skin healing	
Irritability		
Menstrual abnormalities		
In children, slow growth	In children, abnormal genital virilization	
	In children, short stature	
	In children, pseudoprecocious puberty or delayed puberty	

[a] *Features are listed in random order.*
[b] *Cushing's syndrome is more likely if onset of the feature is at a younger age.*

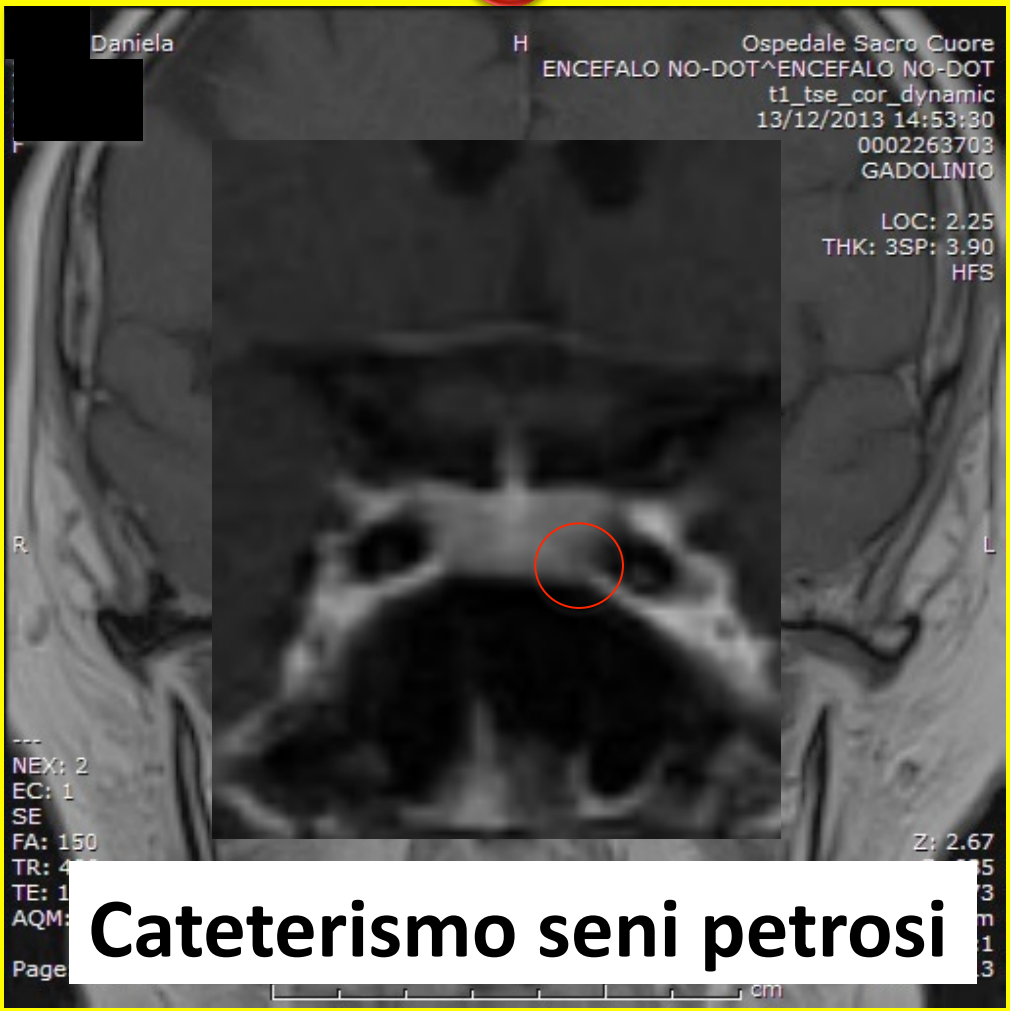
Caso clinico

		Basali	DST 1 mg	DST 2 mg	DST 8 mg	vn
ACTH h.8	ng/L	53				
CORTISOLO h 8:00	nmol/L	574	652	534	399	171-536
CORTISOLO h.18.00	nmol/L	497				64-340
CLU	nmol/d	2358			465	150-1100

Test CRH

Tempi	ACTH (ng/L)	Cortisolo (nmol/L)	ACTH %	Cortisolo %
Base	51	276		
15′	**128**	384	151	
30′	24	**572**		**107**
60′	36	448		

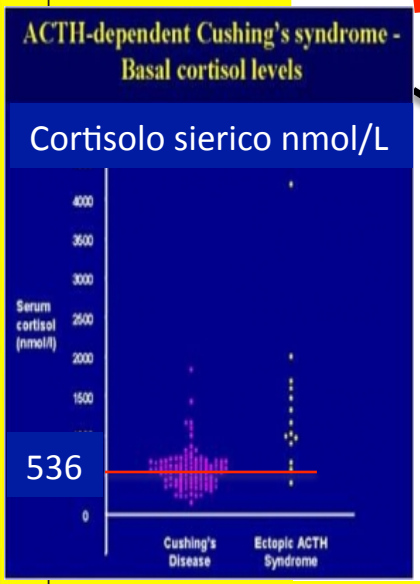
Caso clinico



Cateterismo seni petrosi

Quali esami di screening?

Cortisolo ritmo circadiano



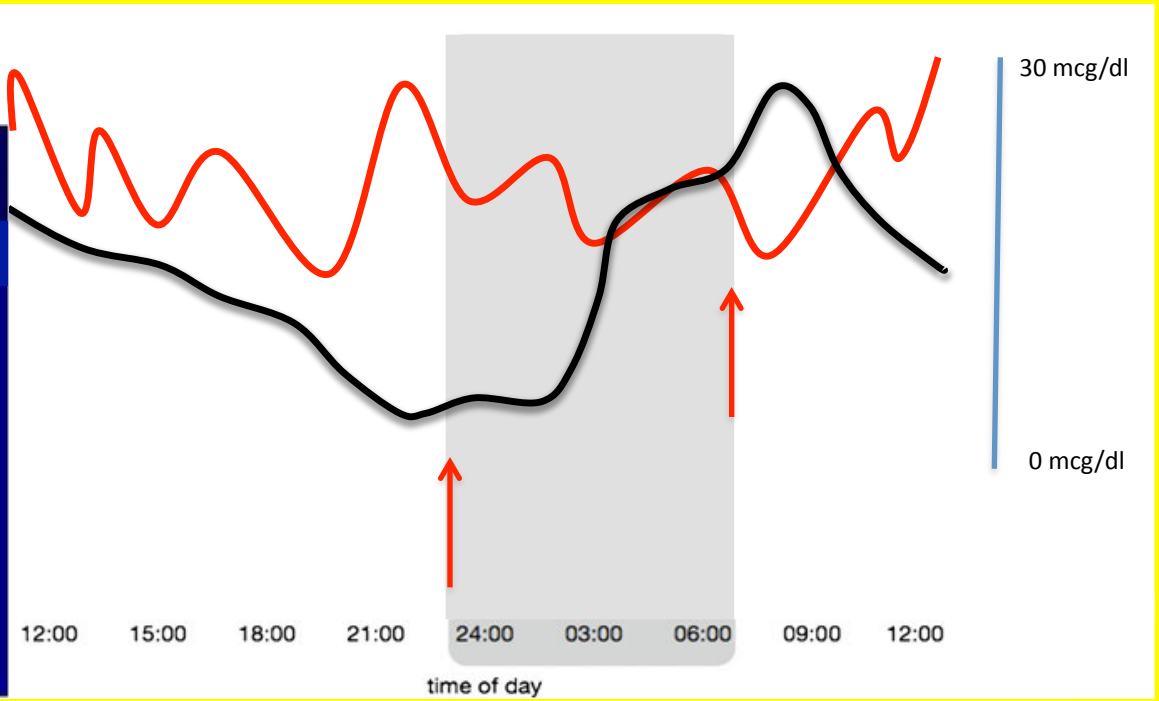
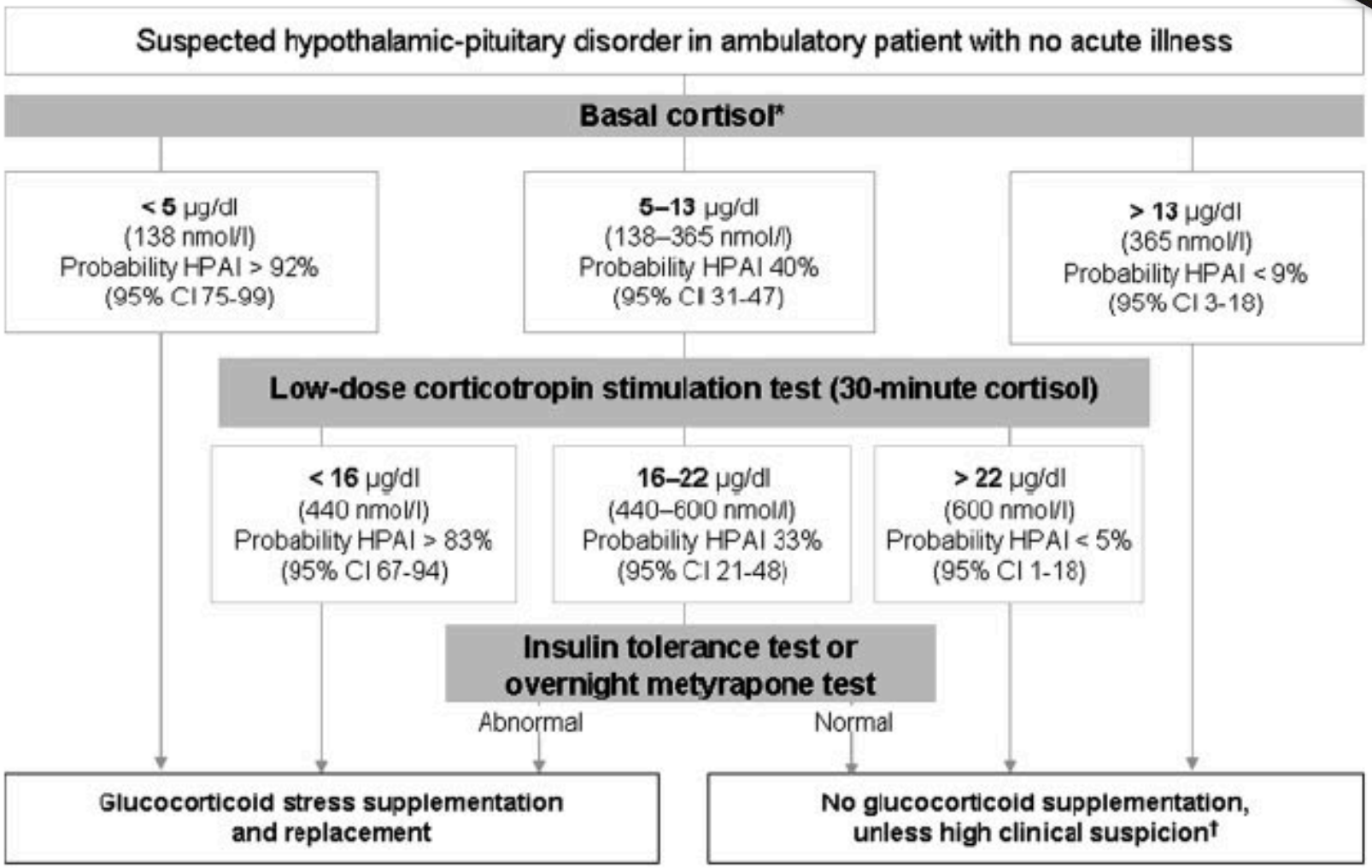


Figure 3 The normal synchronous relationships between sleep and daytime activity and cortisol,

Hickie *et al. BMC Medicine* 2013, **11**:79


Suspected hypothalamic-pituitary disorder in ambulatory patient with no acute illness
Basal cortisol*
< 5 µg/dl
(138 nmol/l)
Probability HPAI > 92%
(95% CI 75-99)
5–13 µg/dl
(138–365 nmol/l)
Probability HPAI 40%
(95% CI 31-47)
> 13 µg/dl
(365 nmol/l)
Probability HPAI < 9%
(95% CI 3-18)
Low-dose corticotropin stimulation test (30-minute cortisol)
< 16 µg/dl
(440 nmol/l)
Probability HPAI > 83%
(95% CI 67-94)
16–22 µg/dl
(440–600 nmol/l)
Probability HPAI 33%
(95% CI 21-48)
> 22 µg/dl
(600 nmol/l)
Probability HPAI < 5%
(95% CI 1-18)
Insulin tolerance test or
overnight metyrapone test
Abnormal
Normal
Glucocorticoid stress supplementation
and replacement
No glucocorticoid supplementation,
unless high clinical suspicion†

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Breaking news

nr. 9 - marzo 2014

PLENADREN PRESCRIVIBILE DA OGGI IN FASCIA H

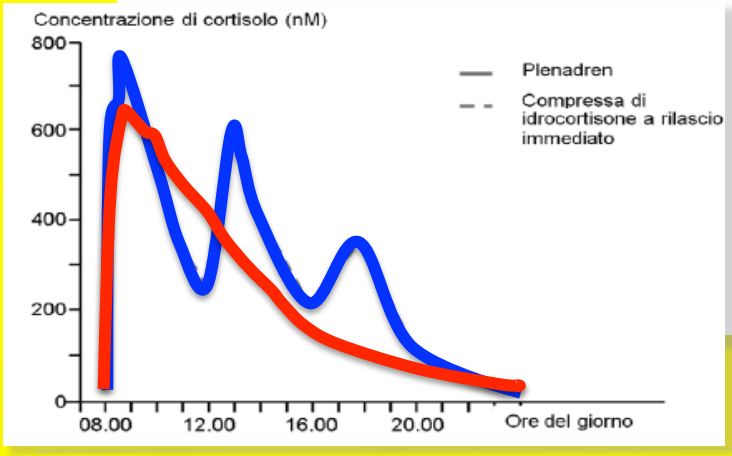
Responsabile Editoriale
Vincenzo Toscano

Da oggi, 3 marzo 2014, il farmaco Plenadren è disponibile in Italia per la prescrizione in fascia H.

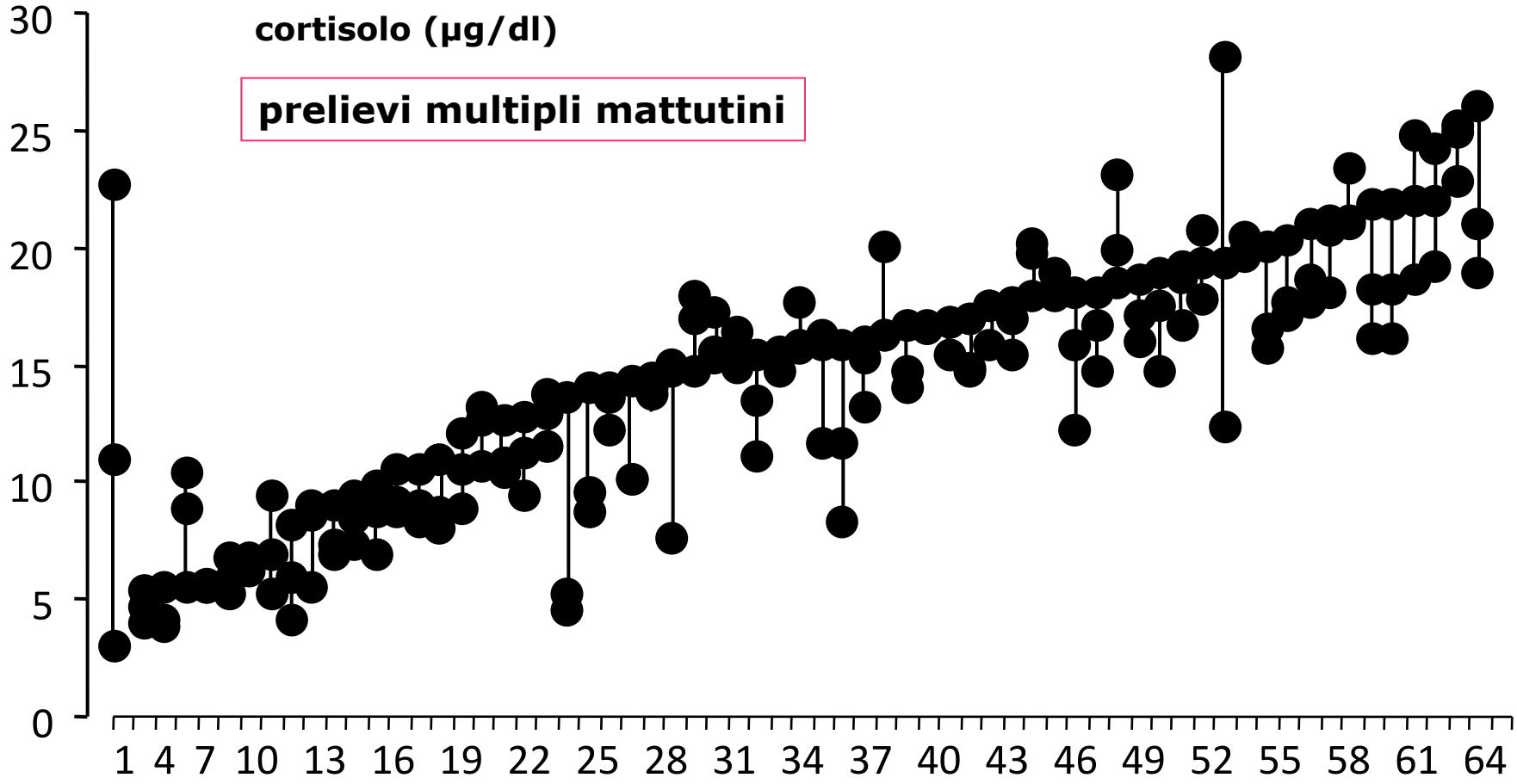
Indicazioni terapeutiche: trattamento dell'insufficienza surrenalica negli adulti.

Classe di rimborsabilità: H.

Classificazione ai fini della fornitura: medicinale soggetto a prescrizione medica limitativa, vendibile al pubblico su prescrizione di centri ospedalieri o di specialisti endocrinologi (RRL).

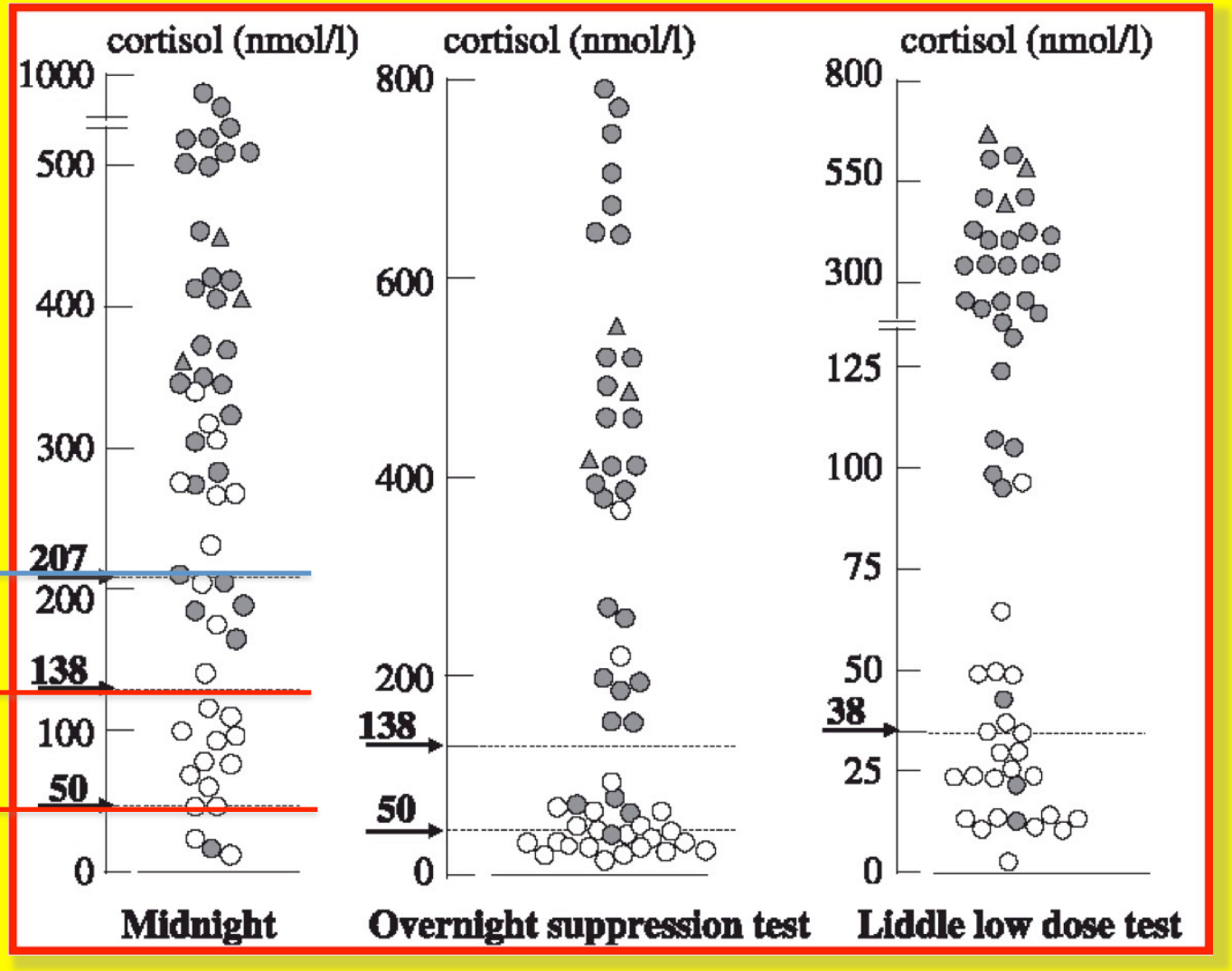


CORTISOLO SIERICO h8 - variabilità



Variabilità individuale 2-13% tra prelievi

Courtesy of Terzolo



7,5 mcg/dl

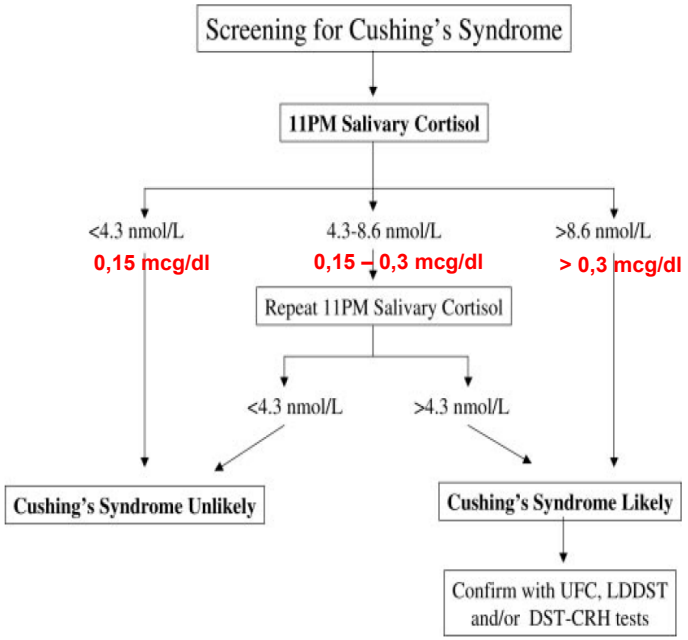
5 mcg/dl

1,8 mcg/dl

CORTISOLO SALIVARE

Table 2 Percentage of positive results with salivary cortisol and urine free cortisol in 11 patients with surgically proven Cushing's syndrome

Patient no.	% Abnormal urine free cortisol	% Abnormal nocturnal salivary cortisol
1	50	78
2	50	29
3	0	14
4	25	100
5	0	100
6	0	100
7	0	100
8	0	100
9	0	71
10	66	33
11	0	100



Kidambi et Al; EJE (2007) 157 725–731

Findling et Raff; JCEM 2006, 91(10):3746

Differentiating between Cushing's disease and pseudo-Cushing's syndrome: comparison of four tests

R A Alwani*, L W Schmit Jongbloed*, F H de Jong, A J van der Lely, W W de Herder and **R A Feelders**

Division of Endocrinology, Room H555, Department of Internal Medicine, Erasmus Medical Centre, PO Box 2040, 3000 CA Rotterdam, The Netherlands
*(R A Alwani and L W Schmit Jongbloed contributed equally to this work)

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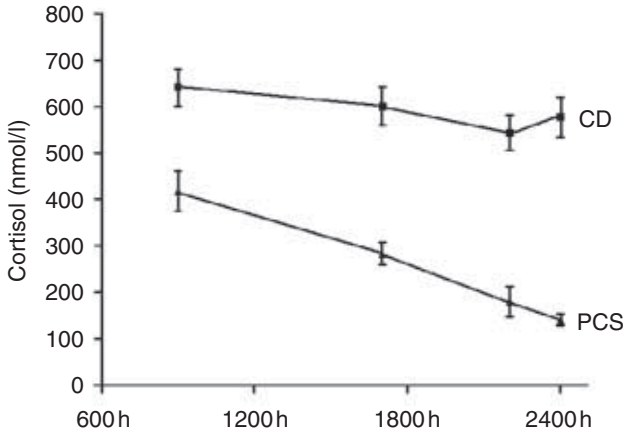
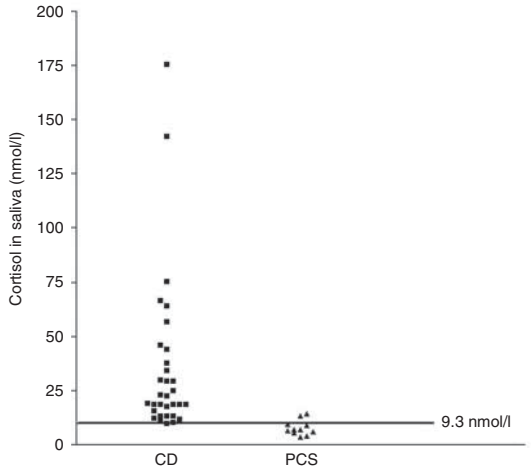
r.alwani@erasmusmc.nl

European Journal of Endocrinology (2014) **170**, 477–486

LNSC level 9.3 nmol/l predicted CD in 94% of pt

Considering its convenience, its high diagnostic accuracy as a first-line screening test as well as its ability to differentiate between CD and PCS, the use of midnight salivary cortisol assessment as a first-choice test seems rational. Depending on the protocol and assay(s) used, it is important for diagnostic centers to validate these tests and their threshold values.





CORTISOLO SALIVARE

➢ **Vantaggi**

- **Buona sensibilità e specificità per la "presentazione moderna" della sindrome di Cushing**
- **Possibilità di campionamenti multipli (3 campioni) in ambiente ambulatoriale, non-stressato**
- **Semplice, poco costoso**

➢ **Svantaggi**

- **Specificità (evening stress, ritmo sonno-veglia, uso di liquirizia e tabacco, contaminazione dei tamponi di raccolta)**
- **Interferenza dei sistemi di raccolta (cotone, polietilene, polistere…)**
- **Livelli di riferimento dipendenti dalla metodica: necessità di «costruire» livelli di riferimento locali su larga fascia di popolazione**

DST 1 mg overnight

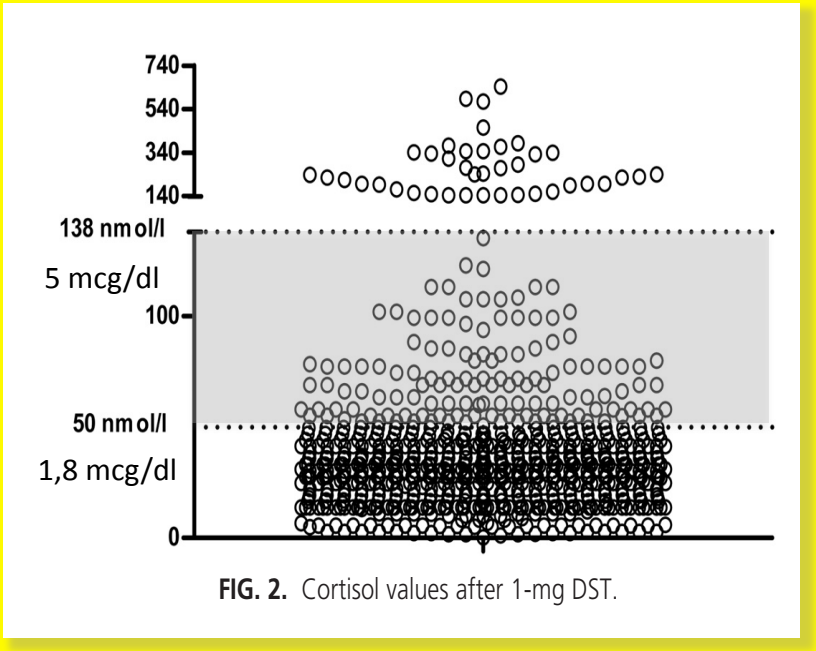


FIG. 2. Cortisol values after 1-mg DST.

Cushing probabile

Cushing improbabile

Quale cut-off?

Terzolo *et al.* J Clin Endocrinol Metab, October 2012, 97(10):3467–3475

TABLE 3. Selected drugs that may interfere with the evaluation of tests for the diagnosis of Cushing's syndrome[a]

Drugs that accelerate dexamethasone metabolism by induction of CYP 3A4

- Phenobarbital
- Phenytoin
- Carbamazepine
- Primidone
- Rifampin
- Rifapentine
- Ethosuximide
- Pioglitazone

Drugs that impair dexamethasone metabolism by inhibition of CYP 3A4

- Aprepitant/fosaprepitant
- Itraconazole
- Ritonavir
- Fluoxetine
- Diltiazem
- Cimetidine

Drugs that increase CBG and may falsely elevate cortisol results

- Estrogens
- Mitotane

Drugs that increase UFC results

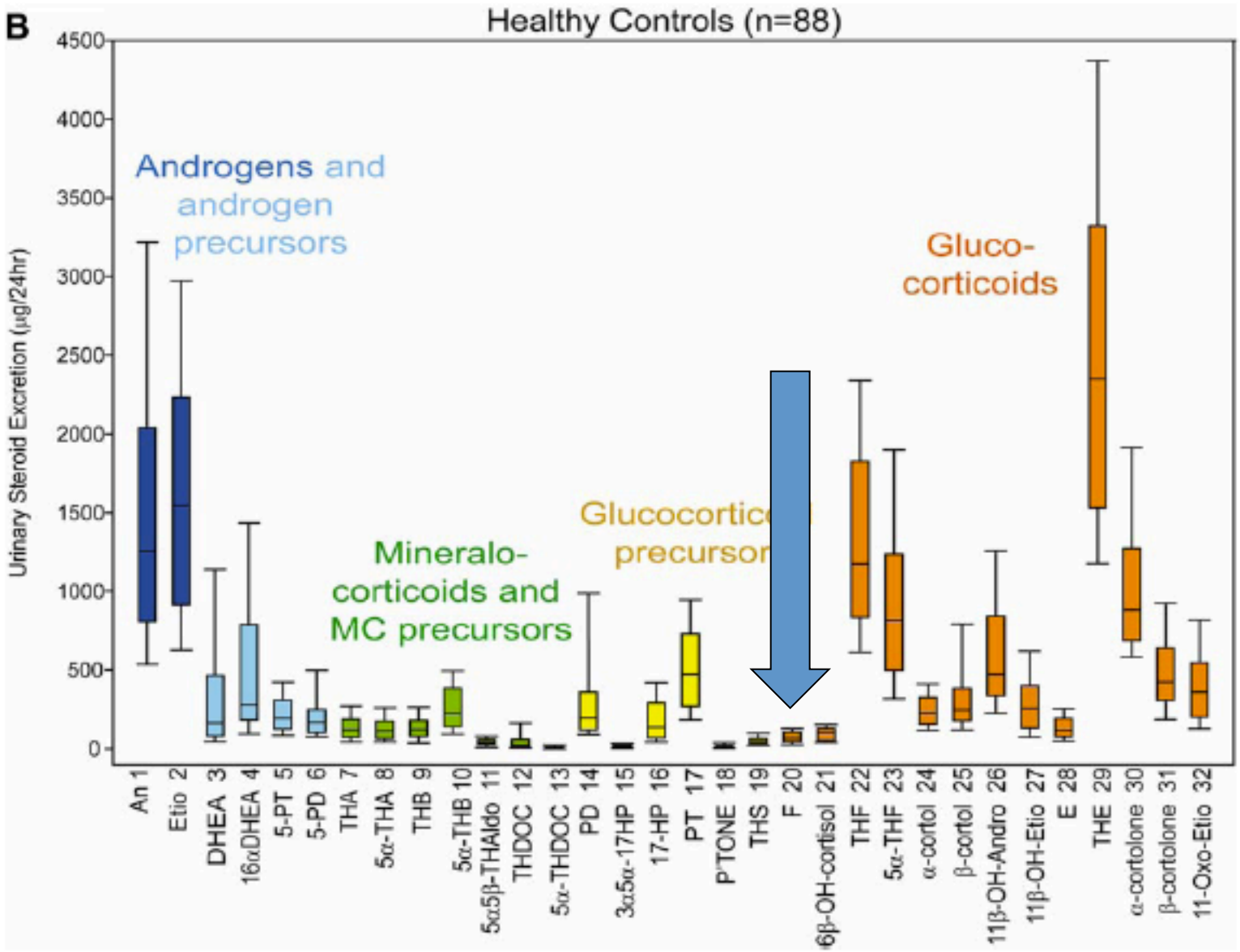
- Carbamazepine (increase)
- Fenofibrate (increase if measured by HPLC)
- Some synthetic glucocorticoids (immunoassays)
- Drugs that inhibit 11β-HSD2 (licorice, carbenoxolone)

Falsi positivi

Falsi negativi

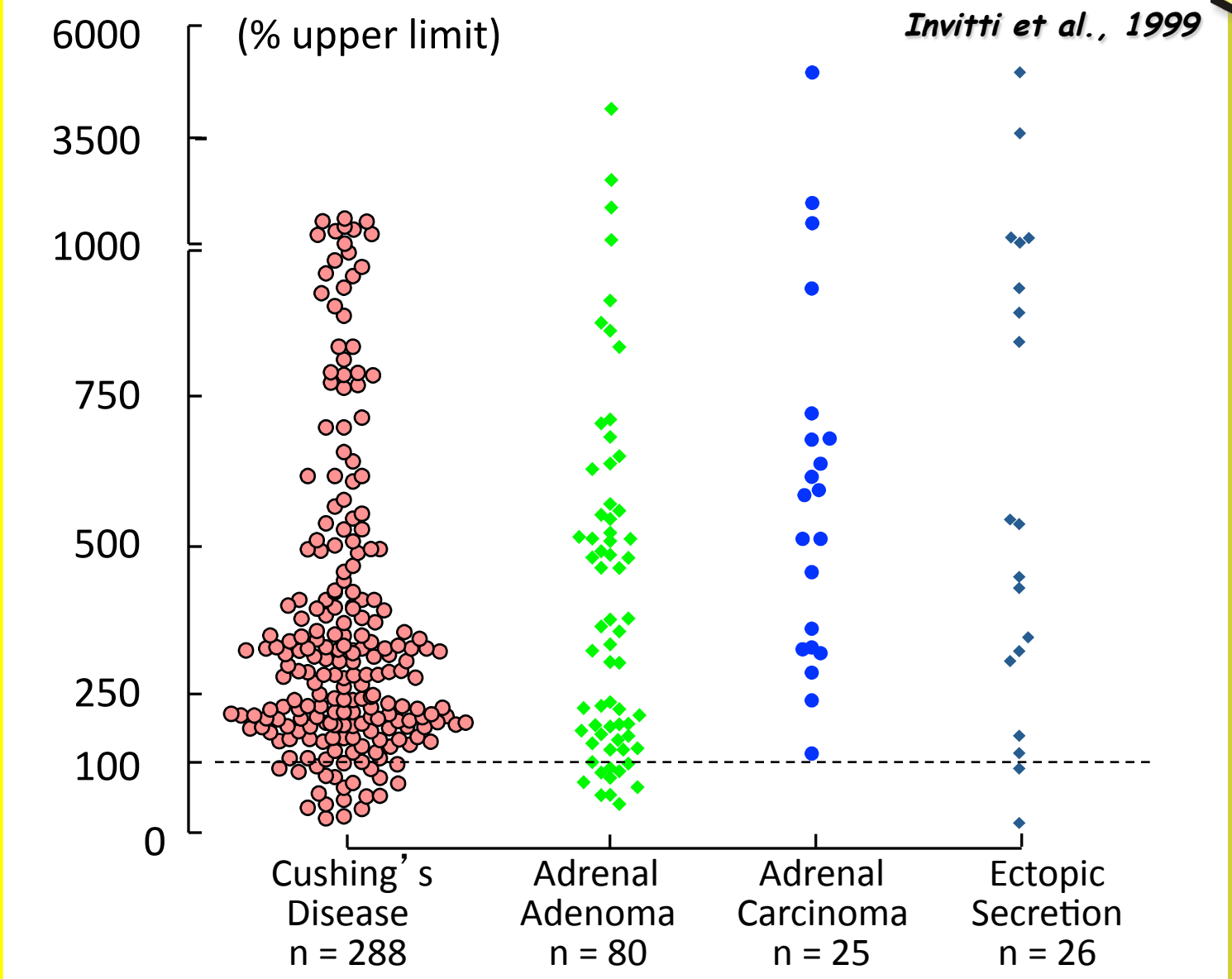
Falsi positivi

Falsi positivi



Arlt et al., 2011

UFC IN PATIENTS WITH CUSHING'S SYNDROME



The Diagnosis of Cushing's Syndrome:

An Endocrine Society Clinical Practice Guideline

Initial testing

3.4. For the initial testing for Cushing's syndrome, we recommend one of the following tests based on its suitability for a given patient (Fig. 1) (1 | ⊕○○○):

3.4.1. Urine free cortisol (UFC; at least two measurements)

3.4.2. Late-night salivary cortisol (two measurements)

3.4.3. 1-mg overnight dexamethasone suppression test (DST)

3.4.4. Longer low-dose DST (2 mg/d for 48 h)

DIAGNOSI di SINDROME di CUSHING

- cortisolo libero urinario (x 2 volte; escludere interferenze)
- cortisolo salivare/sierico alle h 23-h24
- DST 1 mg / 2 mg (cut – off variabile)
- test al CRH / CRH-DST / CRH-Desmopressina
- DST 8 mg

Scegliere il test più adatto alla situazione clinica in esame, eventualmente ripetendolo, secondo le disponibilità locali

NEL POSTINTERVENTO

remissione

- cortisolo libero urinario
- cortisolo salivare/sierico (< 2 mcg/dl) alle h8
- Test ACTH

recidiva

- cortisolo libero urinario
- cortisolo salivare/sierico alle h 23-h24
- cortisolo sierico dopo DST

DURANTE TERAPIA FARMACOLOGICA

- cortisolo libero urinario
- cortisolo salivare/sierico alle h24
- cortisolo sierico dopo DST

The Diagnosis of Cushing's Syndrome:

An Endocrine Society Clinical Practice Guideline

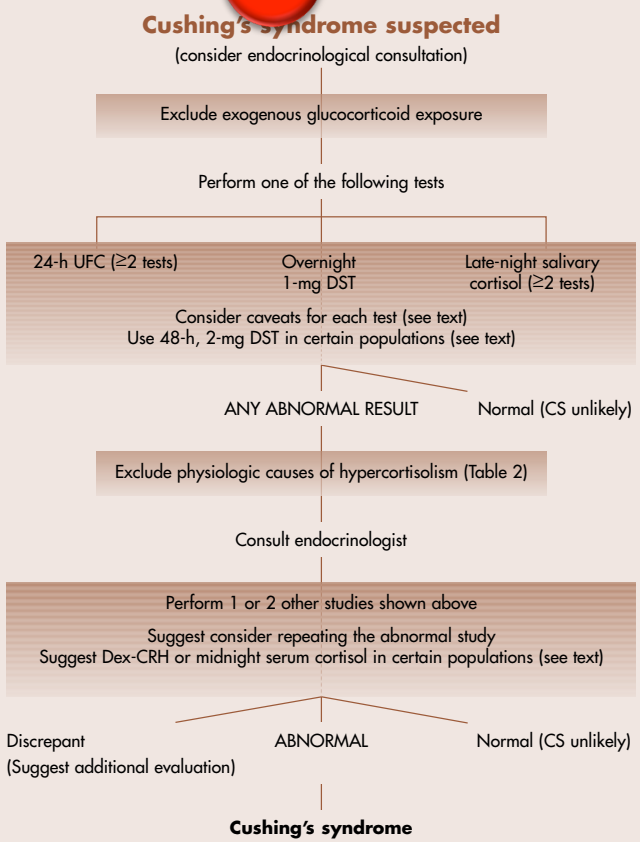


Figure 1. Algorithm for testing patients suspected of having Cushing's syndrome (CS). All statements are recommendations except for those prefaced by suggest. Diagnostic criteria that suggest Cushing's syndrome are UFC greater than the normal range for the assay, serum cortisol greater than 1.8 μg/dl (50 nmol/liter) after 1 mg dexamethasone (1-mg DST), and late-night salivary cortisol greater than 145 ng/dl (4 nmol/liter).

Terapia Farmacologica: quando e cosa ?