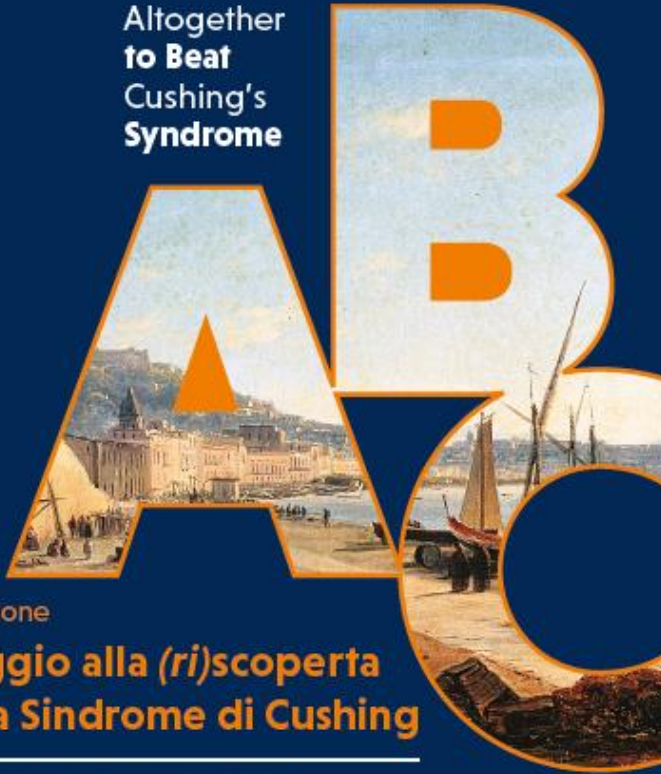




UNIVERSITA' DEGLI STUDI DI NAPOLI FEDERICO II
Dipartimento di Medicina Clinica e Chirurgia

Altogether
to Beat
Cushing's
Syndrome



5ª Edizione

**Viaggio alla (ri)scoperta
della Sindrome di Cushing**

Napoli, 10-12 Aprile 2017

Centro Congressi Federico II - Via Partenope, 36

Coordinatori Scientifici

Annamaria Colao, Rosario Pivonello

SIMPOSIO 2

L' INSUFFICIENZA SURRENALICA SECONDARIA

Moderatori: Gianluca Aimaretti, Alfredo Scillitani

Conclusioni & Open Issues

Alessandro Ciresi

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IL RITMO CIRCADIANO DEL CORTISOLO (A. Isidori)



- Cortisol has a **distinct circadian rhythm** and acts as a secondary messenger synchronizing the central to peripheral clocks, hence playing a **key role in biological processes**.
- The circadian rhythm of cortisol is important for health in humans, and there is evidence of **deleterious effect when this rhythm is disrupted**
- Many of the symptoms that patients with AI complain of such as fatigue, sleep disturbance and poor concentration are seen when the cortisol circadian **rhythm is disrupted in jetlag**
- However, the relationship between cortisol profiles and **long-term health outcomes** is likely to be complex.

Open issues:

- Although development of **delayed release oral preparations** has sought to overcome the inability to mimic accurately the diurnal rhythm of cortisol with current oral replacement therapy, there has been little attention on the **ultradian rhythm** of glucocorticoids (average of 19 peaks/daily) and its relevance for replacement therapy and associated cardio-metabolic comorbidity
- Role of **continuous subcutaneous hydrocortisone infusion (CSHI)** ?

Continuous subcutaneous hydrocortisone infusion (CSHI)

PRO:

- Viable alternative in **patients unable** to take oral steroids.
- Patient **acceptability** was high, with patients preferring to remain on pump treatment (case reports)
- Hospital admissions were reduced in response to pump therapy, which compensated for the increased **treatment cost**.
- The **daily dosage** of hydrocortisone can be reduced by using pump therapy
- Patients with CSHI replacement had a more **stable night-time glucose** level compared with OHC without compromising insulin sensitivity
- Main indication in **CAH**, given that supraphysiologic glucocorticoid doses are often needed to optimally suppress the androgen overproduction.



CONTRA:

- Only a **few data** in primary AI or CAH
- **Training**
- The use of an invasive subcutaneous cannula, which may predispose to local **site infections**, limit physical activity or dislodge and cause **interruption** of steroid delivery
- In the only double-blind study, there was **no clear impact on patients' well-being**. However, this was a small group of patients with good baseline quality of life.
- Selected patients (**costs!**)
- The potential **long-term benefits** on cardiovascular risk factors, QoL and psychological well-being have yet to be examined

**LA TERAPIA CON GLUCOCORTICOIDI:
FARMACI CONVENZIONALI E NUOVE PROSPETTIVE TERAPEUTICHE
(C. Simeoli)**



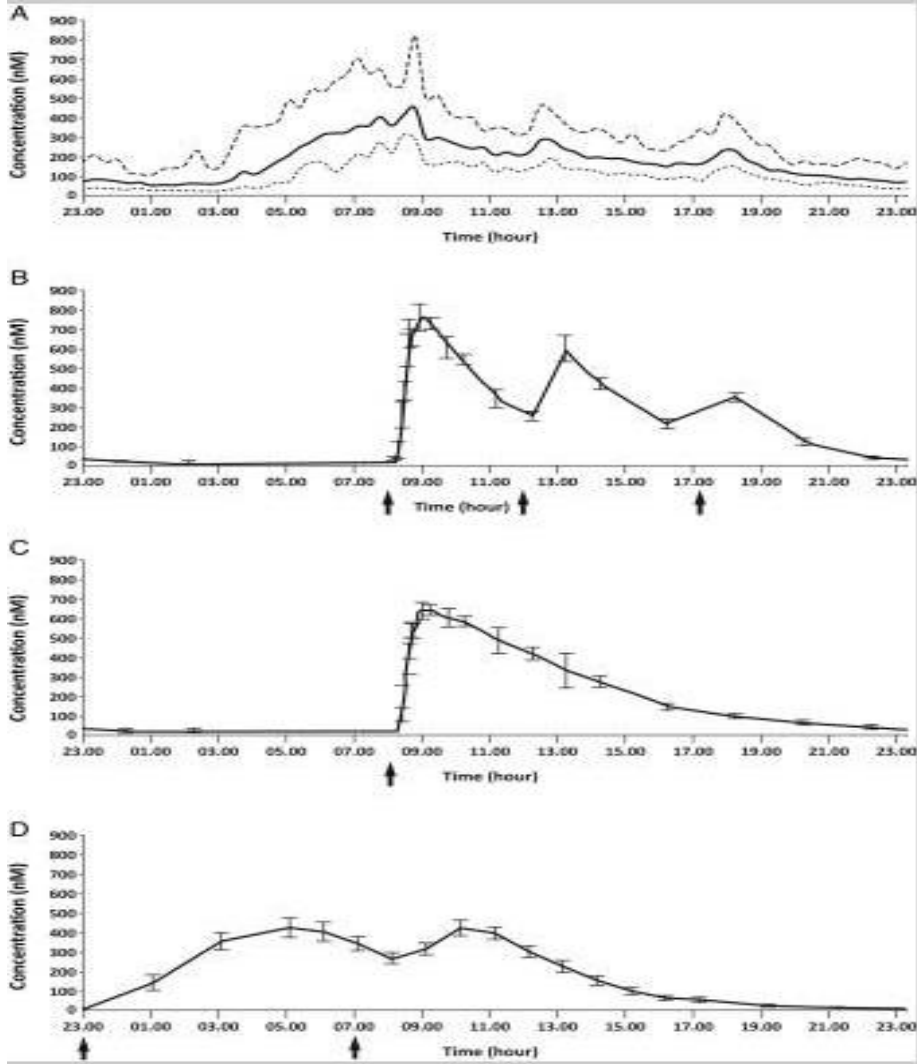
- A major limitation is that **it fails to replace cortisol in a physiological manner.**
- Circadian misalignment has been associated with ill-health and so **nonphysiological glucocorticoid treatment** could explain the increased mortality rate, **poor quality of life and metabolic complications** in patients suffering from AI.

LA TERAPIA CON GLUCOCORTICOIDI: FARMACI CONVENZIONALI E NUOVE PROSPETTIVE TERAPEUTICHE (C. Simeoli)



Limits:

- The expectation is that a once-daily Plenadren regime will improve adherence and quality of life, although this **remains to be demonstrated in blinded and extensive trials.**
- **Dose titration**
- **Costs**
- The dual-release **Plenadren** allows a unique morning intake and closely mimics the circadian rhythm of cortisol secretion, except for the physiological **morning cortisol peak**, which is not well mimicked.
- **Chronocort**, a multiparticulate formulation with sustained-release properties replaces endogenous cortisol in a near-physiologic manner and fully restores the end of night cortisol peak. A **twice-daily** Chronocort regimen was effective in controlling androgen excess in adults with CAH.



Physiological cortisol rhythm

HC (3-dose regimen)

Plenadren

Chronocort (2-dose regimen)

LA TERAPIA CON GLUCOCORTICOIDI: FARMACI CONVENZIONALI E NUOVE PROSPETTIVE TERAPEUTICHE (C. Simeoli)



Open issues:

- “*Longer-acting GCs only in **selected cases** (non-availability, poor compliance, convenience) “ (Fleseriu, JCEM 2016). **Which patient is the real target** of delayed release oral preparations?*
- The majority of data regarding physiological glucocorticoid replacement is from adult patients and there is a need for further studies in **paediatric patients** with AI, who may represent the real target (to date non-refundable for children)
- **Long-term effects** on morbidity and mortality

Controversial data on QoL :

- **Higher conventional GC** doses may wrongly give clinical health?
- The stronger **lack of DHEA** could be a causative factor? DHEA deficiency has been proposed as a potential explanation for a lack of well-being.

IL WORK-UP DIAGNOSTICO: ACTH-Test DOSI STANDARD VERSUS BASSE DOSI (F. Ceccato)



- Its diagnostic value relies on the assumption that chronic ACTH deficiency results in **adrenal atrophy** and therefore diminished response to exogenous acute ACTH stimulation.
- The SST should not be used to assess for **central AI** therefore **for at least 4–6 weeks** post pituitary insult (e.g. surgery, TBI or apoplexy).
- Cortisol response to cosyntropin **varies considerably among healthy persons**.
- The cosyntropin test performs well in patients with primary AI but the **lower sensitivity** in patients with secondary AI necessitates use of tests involving stimulation of the hypothalamus if the **pretest probability is sufficiently high**.

The Endocrine Society Guideline suggests for diagnosis of **PAI**:

- **standard dose (250 µg** for adults and children ≥ 2 y) iv corticotropin stimulation (**30 or 60 min**) test. Peak cortisol levels below 500 nmol/L (18 µg/dL) (assay dependent) at 30 or 60 minutes indicate adrenal insufficiency (2 | ⊕ ⊕ ○○)”
- **low-dose (1 µg)** corticotropin test **only when the substance itself is in short supply.** (2 | ⊕ ⊕ ○○)

In **SAI** both tests are **adequate to rule in, but not rule out, SAI.**

Low-dose test was superior to standard-dose test for diagnosing chronic HPAI (Metaanalysis, JCEM 2008). The confidence in these estimates is low to moderate because of the likely risk of **bias**, heterogeneity, and imprecision (Ospina, JCEM 2016)

CHILDREN: - There are **no randomised trials**

- SSST resulted in **higher specificity**

- The LDSST had a **higher sensitivity** (86% vs 81%) but a lower specificity (88% vs 99%) than the SSST, but there was **high heterogeneity from studies**

The choice of either SSST or LDSST should be individualised **based on clinical judgement** for each patient (Ng SM, Arch Dis Child. 2016)

IL WORK-UP DIAGNOSTICO: ACTH-Test DOSI STANDARD VERSUS BASSE DOSI (F. Ceccato)



Open issues:

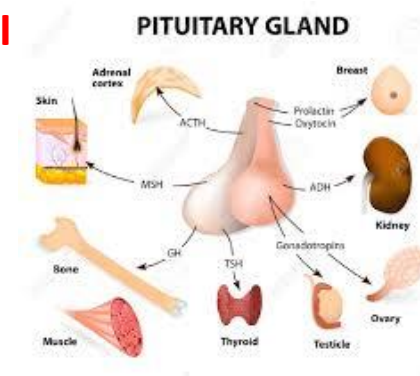
- ❑ 250- μ g cosyntropin testing is a **supraphysiologic stimulus (pharmacological dose)** to assess adrenocortical functional reserve and it may induce many **false-normal responses**, especially in patients with mild or recent-onset SAI.
- ❑ Gender or BMI-dependent cut-off? (**Dosage weight-based?**)
- ❑ **Time 30' sufficient when 1 μ g is used?** (Endocrine Society Guideline, JCEM, 2016)
Peak more frequent at 30', but in some case just at 60' (time 30' overestimates AI?).
Overweight and obese individuals tended to peak at 30'
- ❑ **Salivary vs. plasmatic** cortisol during ACTH test

No single test is able to correctly identify all patients with SAI: mild SAI can be missed, while even healthy individuals might show abnormal values. Therefore, **clinical judgment** remains important and **follow-up** is crucial for assessment of ACTH deficiency.

L' INSUFFICIENZA SURRENALICA SECONDARIA: RELAZIONE CON GLI ALTRI DEFICIT IPOFISARI (C. Di Somma)

Endocrine Society Guideline:

We suggest evaluating patients with CH for AI **before starting L-T4 therapy.**



We suggest that when clinicians assess adrenal reserve or the adequacy of HC replacement, they take into consideration that total serum cortisol level can be elevated due to the **effects of estrogen** on corticosteroid-binding globulin (CBG)

We suggest testing HPA axis functionality **before and after starting GH** replacement in patients who are not receiving GC replacement and who have demonstrated apparently normal pituitary-adrenal function (**GHD can mask and GHT can unmask AI**)

Open issues:

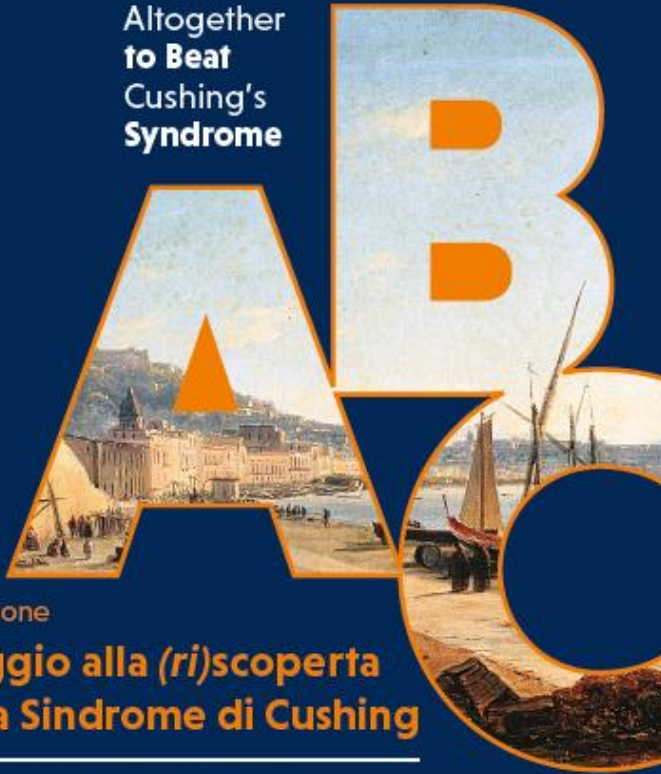
- How frequently?
- How (morning cortisol, ITT, ACTH) ?





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