Malattie di Addison Terapie innovative

Andrea M. Isidori

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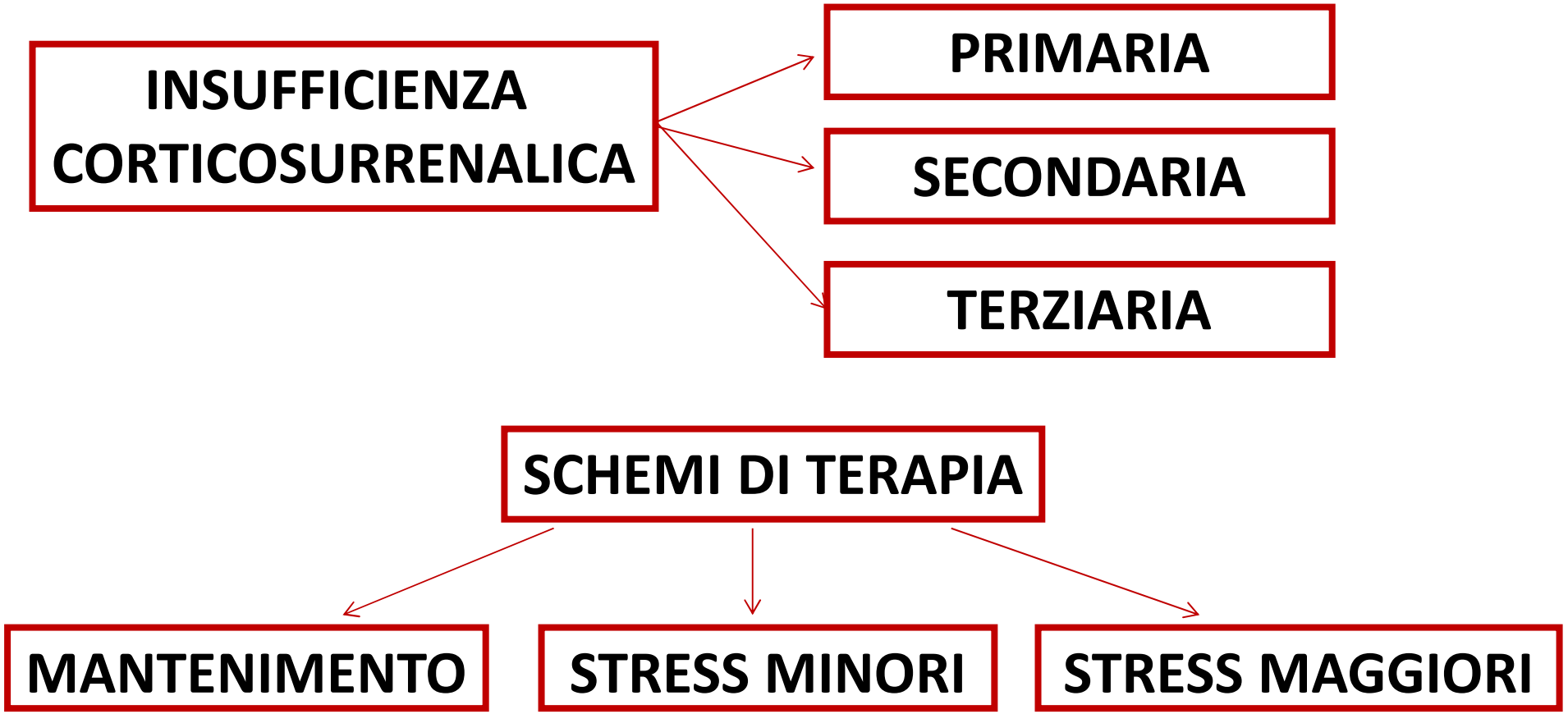
SAPIENZA
UNIVERSITÀ DI ROMA

MCEL
MOLECULAR AND CLINICAL ENDOCRINOLOGY LAB

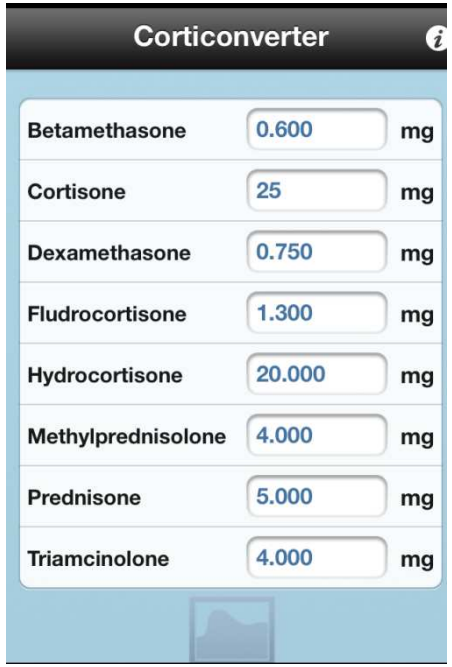
TERAPIA SOSTITUTIVA CON GLUCOCORTICOIDI



EDUCAZIONE DEL PAZIENTE E DEI FAMILIARI

Arlt W. Allolio B. Lancet 2003
Charmandari et al, Lancet 2014

SCHEMA DI TRATTAMENTO



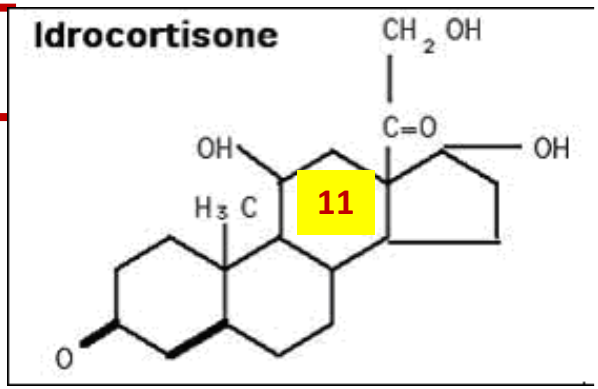
1. Terapia per la deficienza di glucocorticoidi

Cortisone acetato 25–37·5 mg die (BID-TID)
Idrocortisone 15–25 mg die (BID-TID)

Steroide	Dose equivalente (mg)	Potenza relativa anti-infiammatoria	Potenza relativa mineralcorticoidea	Emivita plasmatica (h)	Emivita biologica (h)
Cortisone acetato	25	0.8	2	0.5	8-12
Idrocortisone	20	1	2	1.5-2	8-12
Metilprednisolone	4	5	0	1.5-3	18-36
Prednisone	5	4	1	1	18-36
Prednisolone	5	4	1	2-3.5	18-36
Triamcinolone	4	5	0	3.5-4	18-36
Betametasone	0.6-0.75	20-30	0	5.5	36-54
Desametasone	0.75	20-30	0	2-3.5	36-54

TERAPIA CONVENZIONALE CON GLUCOCORTICOIDI

IDROCORTISONE: farmaco di prima scelta



- **Ormone biologicamente attivo:**

  idrossilazione in posizione 11

- **Concentrazione plasmatica:**

  picco dopo 1 ora dalla somministrazione;

  dosabile nel sangue per circa 2 ore;

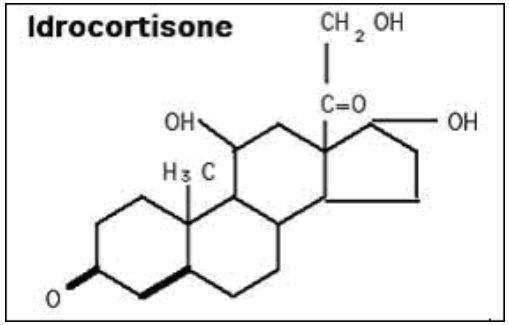
  i suoi metaboliti sono misurabili fino a 4-7 ore

- **Legato a proteine per circa il 90% (CBG e albumina) Forma attiva 5-10%**

- **Assorbimento intestinale ad opera della glicoproteina P**

Farmaci che aumentano i livelli di CBG e che possono falsamente elevare i livelli di cortisolo
Estrogeni
Mitotane

IDROCORTISONE



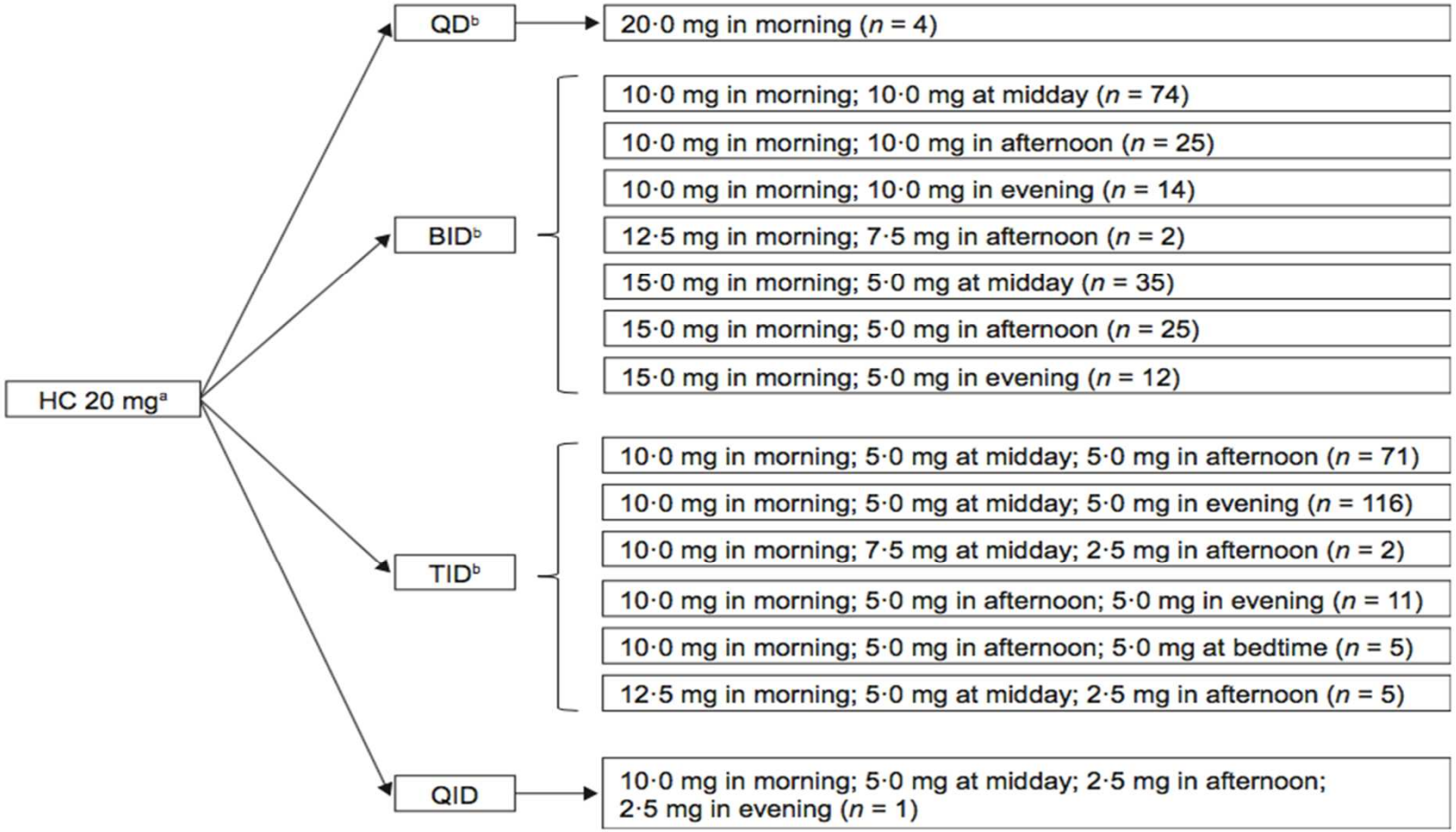
- **La fase I del metabolismo dell'idrocortisone è epatica (citocromo CYP3A4, isoenzima del citocromo P450):**

  Riduzione e Ossidazione

- **La fase II: glucuronidazione e rilascio nel circolo enteroepatico ed eliminato tramite il circolo ematico per via renale (70-80%) e parte nelle feci (20-30%)**

Farmaci che accelerano il metabolismo mediante induzione del CYP3A4
Fenobarbitale
Fenitoina
Carbamazepina
Primidone
Rifampicina
Etosuccimide
Pioglitazone
Farmaci che riducono il metabolismo mediante inibizione del CYP3A4
Itraconazolo
Ritonavir
Fluoxetina
Diltiazem
Cimetidina

Variazioni sul tema



CORTISONE ACETATO

PRO FARMACO

Biologicamente attivo solo dopo idrossilazione nel fegato: l'80% è trasformato in cortisolo ad opera della 11β-HSD1 con perdita di circa 1/5 della dose efficace

Segue la **stessa via di metabolizzazione dell'idrocortisone**

CORTISONE ACETATO versus IDROCORTISONE

- **Minore attività glucocorticoide e relativa mineralcorticoide**
- **Picco di massima concentrazione plasmatica ridotto**
- **Insufficienza epatica: bassa idrossilazione nel fegato**
- **Deficit di 11β-HSD1: impossibile attivare il cortisone (molto rara)**
- **Sostanze endogene ed esogene (acidi biliari, carbenoxolone, liquirizia) possono inibirne l'attività**

ALTRI GLUCOCORTICOIDI

- **RITMO CIRCADIANO NON RISPETTATO**
- **AUMENTO DEGLI EFFETTI COLLATERALI**

Steroide	Dose equivalente (mg)	Potenza relativa anti-infiammatoria	Potenza relativa mineralcorticoidea	Emivita plasmatica (h)	Emivita biologica (h)
Metilprednisolone	4	5	0	1.5-3	18-36
Prednisone	5	4	1	1	18-36
Prednisolone	5	4	1	2-3.5	18-36
Betametasone	0.6-0.75	20-30	0	5.5	36-54
Desametasone	0.75	20-30	0	2-3.5	36-54

3.3 As an alternative to hydrocortisone, we suggest using prednisolone (3–5 mg/d), administered orally once or twice daily, especially in patients with reduced compliance. (2|⊕◯◯◯)

Bornstein (chair) et al Guidelines on Primary Adrenal Insufficiency J Clin Endocrinol Metab, February 2016,

Endocrine Connections
(2017) **6**, 1–8

Prednisolone is associated with a worse lipid profile than hydrocortisone in patients with adrenal insufficiency

Marcus Quinkler[1], Bertil Ekman[2], Claudio Marelli[3], Sharif Uddin[4], Pierre Zelissen[5] and **Robert D Murray[6] on behalf of the EU-AIR Investigators**

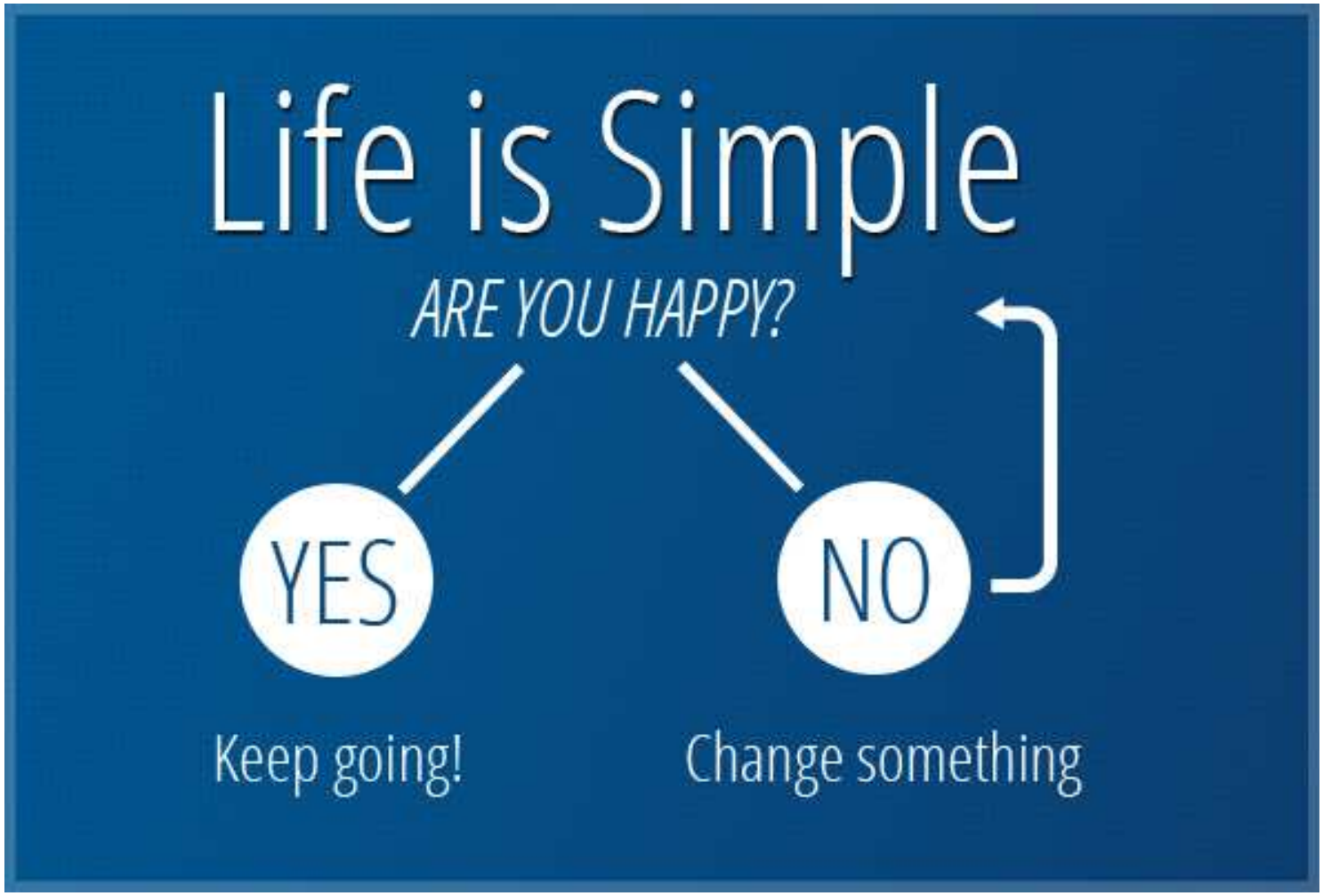
Table 2 Cohorts of patients with AI from the EU-AIR with prednisolone or hydrocortisone replacement therapy used for the matching process (for age, sex, duration and type of disease (PAI or SAI)).

	Before matching		After matching	
Variable	Prednisolone ($n=50$)	Hydrocortisone ($n=909$)	Prednisolone ($n=47$)	Hydrocortisone ($n=141$)
Age (years)	58.5 (16.6)	54.2 (16.2)	58.0 (16.6)	60.0 (14.4)
Duration of disease (years)	25.1 (13.6)	15.4 (11.0)	23.0 (10.3)	23.1 (10.2)
Female (%)	62.0	50.8	61.7	61.7
PAI (%)	40.0	30.9	40.4	40.4

Table 4 Clinical and biochemical characteristics in matched cohorts of patients with AI from the EU-AIR with prednisolone or hydrocortisone replacement therapy.

	After matching	
Variable	Prednisolone ($n=47$)	Hydrocortisone ($n=141$)
Daily dose (mg)	5.0 (0.6)	21.5 (4.8)
Body mass index (kg/m^2)	27.2 (3.9) ($n=44$)	27.8 (5.3) ($n=119$)
Systolic blood pressure (mmHg)	128 (18.1) ($n=47$)	131 (18.0) ($n=133$)
Diastolic blood pressure (mmHg)	77.7 (9.2) ($n=47$)	79.4 (10.2) ($n=133$)
Waist circumference (cm)	99.0 (13.8) ($n=21$)	96.1 (13.9) ($n=86$)
Total cholesterol (mmol/L)	6.3 (1.6)*** ($n=36$)	5.4 (1.1) ($n=82$)
High-density lipoprotein (mmol/L)	1.5 (0.5) ($n=31$)	1.5 (0.4) ($n=76$)
Low-density lipoprotein (mmol/L)	3.9 (1.4)** ($n=34$)	3.2 (1.0) ($n=71$)
HbA1c (%)	5.8 (1.0) ($n=32$)	5.8 (1.0) ($n=81$)
Triglycerides (mmol/L)	1.8 (0.8) ($n=35$)	1.9 (0.9) ($n=82$)
Proportion of patients using statins (%)	25.5	26.9

Data show mean (±S.D.) unless otherwise indicated.
**$P=0.013$; ***$P=0.003$ (two-sample t-tests).


Life is Simple
ARE YOU HAPPY?
YES
NO
Keep going!
Change something

Terapia sostitutiva convenzionale con glucocorticoidi

Mortalità prematura

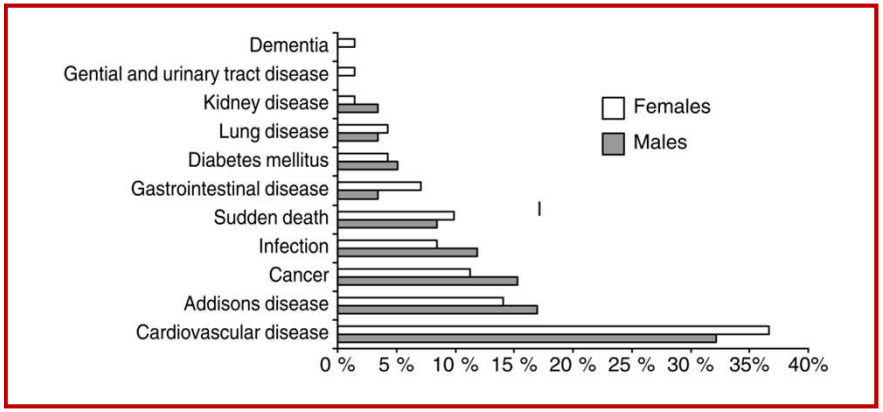
Alta frequenza di ospedalizzazioni/ infezioni

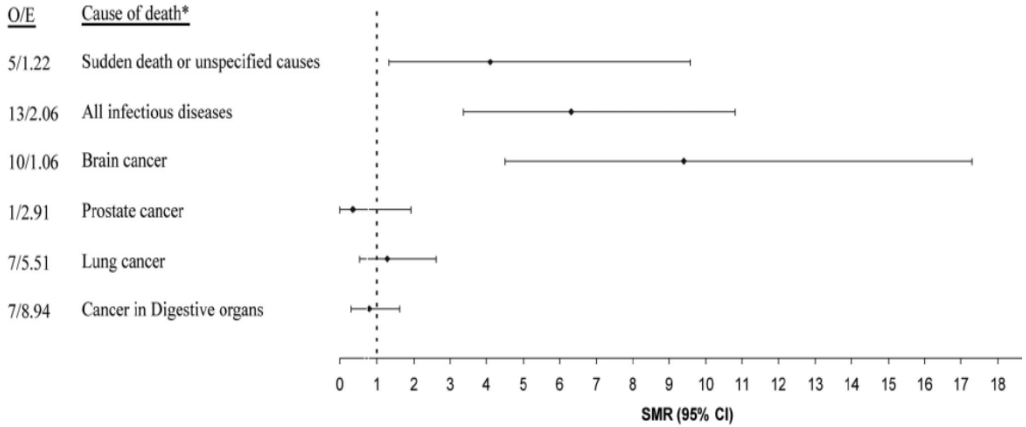
Ridotto benessere e qualità percepita della vita

Alterato profilo metabolico

Steatosi epatica

Ridotta densità minerale ossea





"Infection was the death cause in **10% (5.1– 14.9) opposed to 6.0%** in the general population.**"**

Erichsen MM *et al.* - Mortality in Addison's disease - European Journal of Endocrinology (2009)
Burman *et al* - Deaths Among Adult Patients with Hypopituitarism - J Clin Endocrinol Metab 2013
Bergthorsdottir et al. JCEM 2006, Smans LCCJ et al. ECE 2011, Hahner et al. JCEM 2007
Filipsson et al. JCEM 2007, Zelissen et al. Ann Intern Med 1994; Lövås et al EJE 2009

Clinical Endocrinology (2015) 82, 2–11 doi: 10.1111/cen.12603

REVIEW ARTICLE

Adrenal insufficiency: review of clinical outcomes with current glucocorticoid replacement therapy

Gudmundur Johannsson*, Alberto Falorni†, Stanko Skrtic‡§, Hans Lennernäs¶, Marcus Quinkler**, John P. Monson†† and Paul M.Stewart‡‡

- **Piu'di 40 anni per dimostrare gli effetti collaterali della terapia sostitutiva**
- **Riduzione dell'aspettatitiva di vita e di QoL, aumento della morbidità**
- **Rischio di crisi surrenaliche associate ad infezioni ed altri stress**
- **Rischio di sovradosaggio e fallimento nella gestione complessiva del paziente**

NUOVE STRATEGIE TERAPEUTICHE → **RIDURRE LA DOSE**

NUOVE STRATEGIE TERAPEUTICHE → **MODIFICARE LA MODALITA' DI SOMMINISTRAZIONE**

Reduction in daily hydrocortisone dose improves bone health in primary adrenal insufficiency

Julia Schulz[1], Kathrin R Frey[2], Mark S Cooper[3], Kathrin Zopf[1], Manfred Ventz[1], Sven Diederich[4] and Marcus Quinkler[1,5]

90 PZ: 57 PAI (42 F)
33 CAH (21 F)
Divisi in 3 gruppi: 1) Non modifiche della dose di HC (N=50)
2) Aumento della dose di HC (N=13)
3) Diminuzione della dose di HC (N=27)

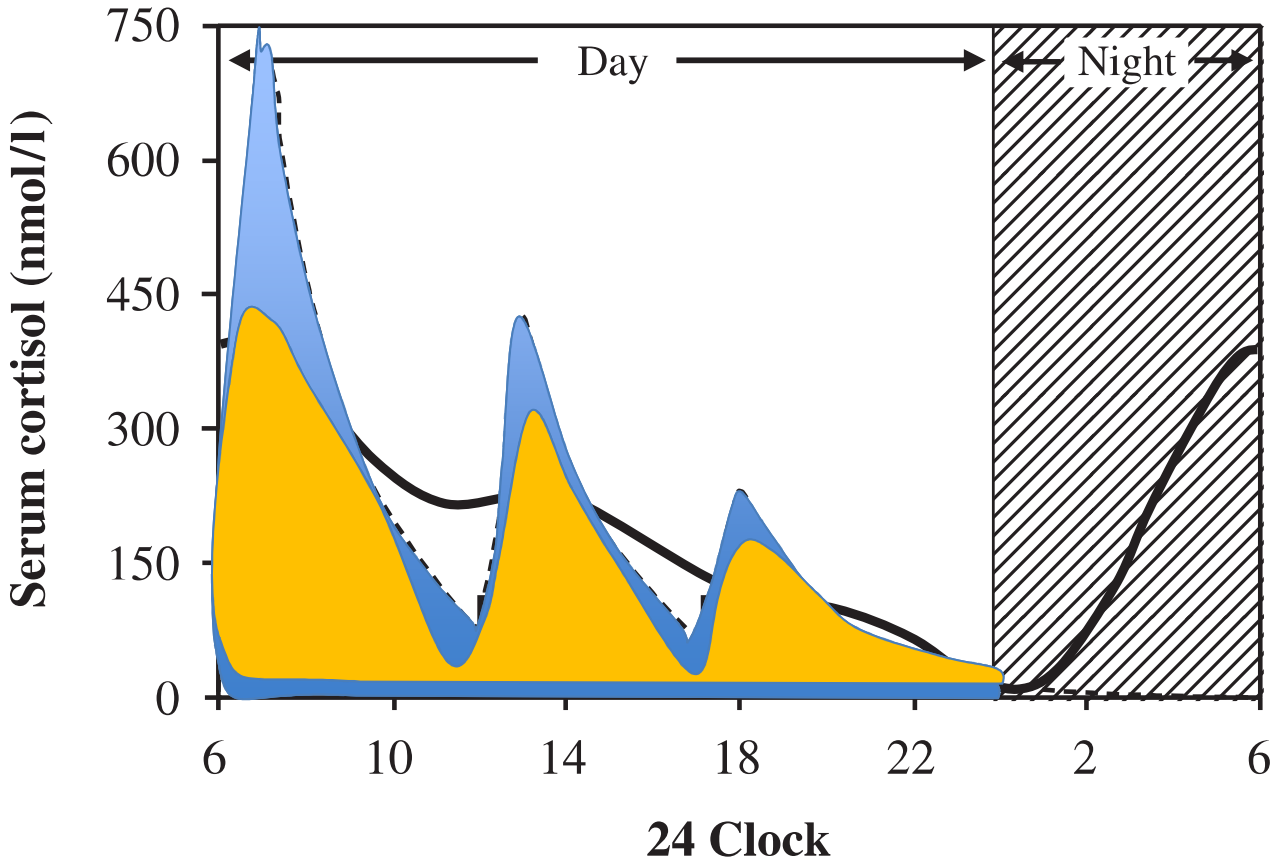
Table 3 Clinical data and bone mineral density (BMD) at baseline and follow-up after 28.7±5.6 months depending on change in daily HC equivalent dose at follow-up in patients with primary adrenal insufficiency (PAI) or congenital adrenal hyperplasia (CAH).

	HC equivalent dose unchanged		HC equivalent dose increased		HC equivalent dose decreased	
	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
n (PAI/CAH)	50 (38/12)	50 (38/12)	13 (6/7)	13 (6/7)	27 (13/14)	27 (13/14)
Sex (male/female)	15/35	15/35	3/10	3/10	9/18	9/18
Age (year)	52.9±15.1	55.2±15.2*	38.7±13.2†	41.2±12.9*,‡	44.4±12.8	46.8±12.8*
BMI (kg/m^2)	26.8±4.1	26.8±4.1	23.2±2.0†	23.7±2.3‡	26.7±5.7	27.1±5.9
Duration of disease (year)	20.3±14.5	22.2±14.4*	25.4±12.3	27.7±12.2*	24.4±14.2	26.5±14.2*
Daily HC-equivalent dose (mg)	25.2±8.2	25.2±8.2	18.7±10.3†	25.9±12.0*	30.8±8.5†	21.4±7.2*
GC-dose per body surface (mg/m^2)	13.9±4.4	13.9±4.4	11.9±7.9	16.2±9.2*	17.3±5.7†	11.8±4.1*
Calcium (2.15–2.65 mmol/l)	2.32±0.1	2.40±0.1*	2.30±0.1	2.47±0.1*	2.32±0.1	2.41±0.1§
Phosphorus (0.8–1.5 mmol/l)	0.93±0.2	0.91±0.2	0.98±0.2	0.94±0.2	0.96±0.2	0.97±0.2
Alkaline phosphatase (35–104 U/l)	57.8±13.7	60.5±15.7	52.6±12.9	55.3±17.2	60.1±21.8	57.7±16.7
Parathyroid hormone (11–67 pg/ml)	35.0±20.4	35.5±15.2	41.8±22.7	47.3±55.9	36.1±23.4	33.4±12.8
25-hydroxyvitamin D_3 (50–250 nmol/l)	61.5±21.3	87.5±25.2*	56.1±25.1	74.6±34.7	56.7±19.4	78.3±24.3*
Z-score lumbar spine (L1–L4)	−0.19±1.2	−0.12±1.2	−0.24±1.1	−0.32±1.3	−0.93±1.2	−0.65±1.5§
Z-score femoral neck	−0.02±1.2	−0.01±1.2	−0.15±1.1	−0.37±1.0§	−0.58±0.9	−0.50±1.0
Z-score greater trochanter	0.11±1.2	0.10±1.3	0.04±1.0	−0.17±1.0	−0.25±1.0	−0.14±1.1
Z-score total hip	0.00±1.1	0.01±1.1	−0.16±0.7	−0.34±0.6	−0.40±1.0	−0.28±1.0§

Z-scores represent age and gender-adjusted SDS. Means±s.d. *P<0.001 vs baseline, †P<0.05 vs 'dose unchanged' baseline, ‡P<0.05 vs 'dose unchanged' follow-up and §P<0.05 vs baseline.

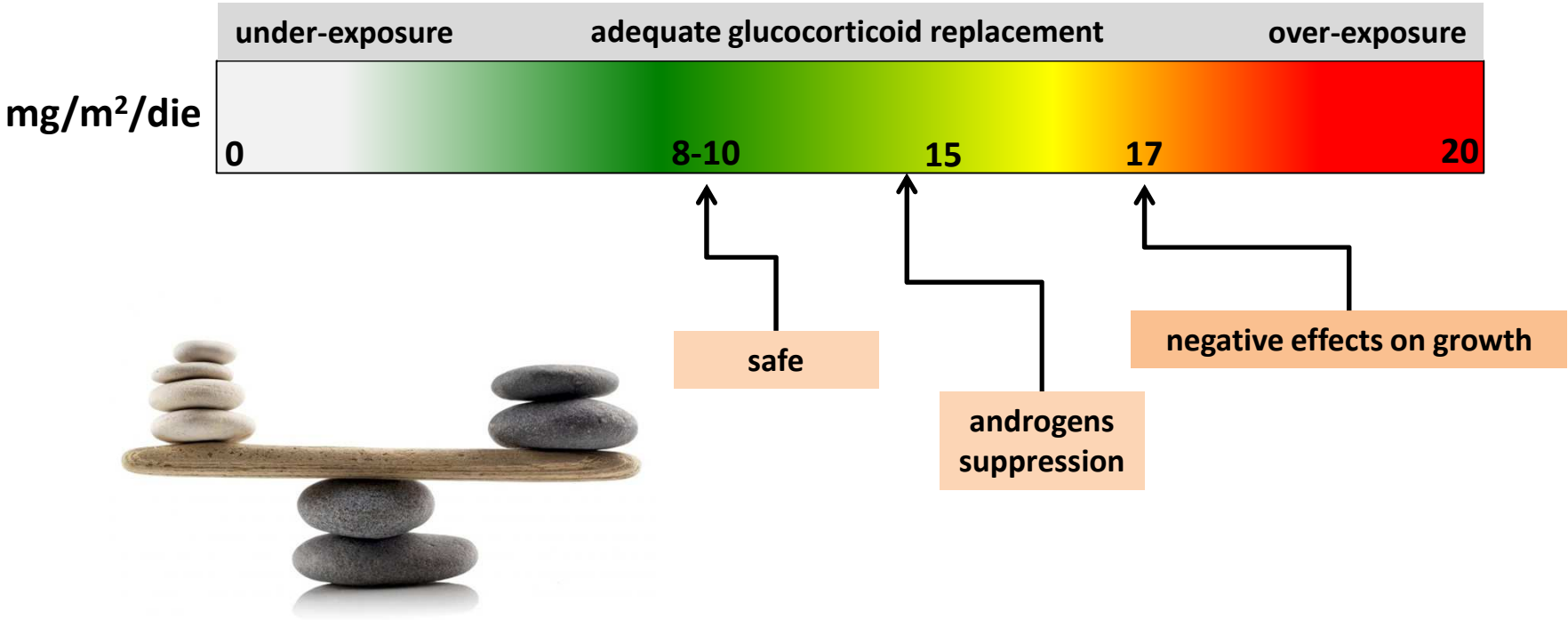
Modification of GC replacement should be undertaken with care

Attempt to reduce AUC of GC exposure by reducing the peak dose might expose the risk toward immune system overreaction and/or chronic inflammatory state



Peak M Mah *Clinical Endocrinology* 2004;61:367–375.

Dosage titration



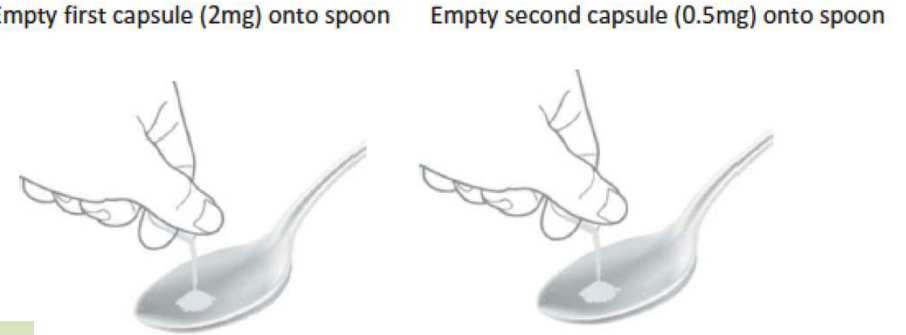
Webb EA et al, Current and novel approaches to children and young people with CAH and AI. **Best practice and Research Clinical Endocrinology and Metabolism 2015**

Novel strategies for dosage titration

the "old"….

Alkindi 0,5 mg granuli in capsule da aprire
Alkindi 1 mg granuli in capsule da aprire
Alkindi 2 mg granuli in capsule da aprire
Alkindi 5 mg granuli in capsule da aprire

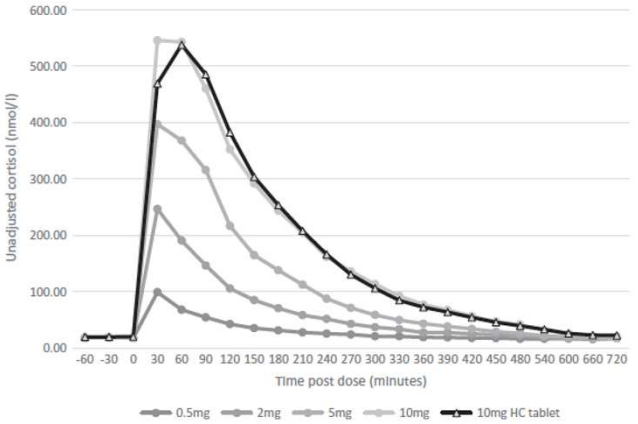
the "new"



Give complete dose (2.5mg) to child following administration instructions

Box 1. Drug summary.

Drug name Hydrocortisone
Phase IV
Indication Replacement therapy of adrenal insufficiency in infants, children, and adolescents (from birth to <18 years old).
Pharmacology description/mechanism of action
Synthetic form of naturally occurring glucocorticoid hormone cortisol. Pleotropic effects through activation of the glucocorticoid receptor in multiple tissues.
Route of administration Oral
Pivotal trial(s) Infacort 003 Single-arm pharmacokinetic study of drug in children aged from birth to 6 years with adrenal insufficiency. To our knowledge, this is the first published interventional pharmacokinetic study in this age and patient group.



Porter J et al, Immediate release granule formulation of HC, Alkindi, for treatment of pediatric AI. **Expert review of endocrinology and metabolism 2018**


talk about what's new!

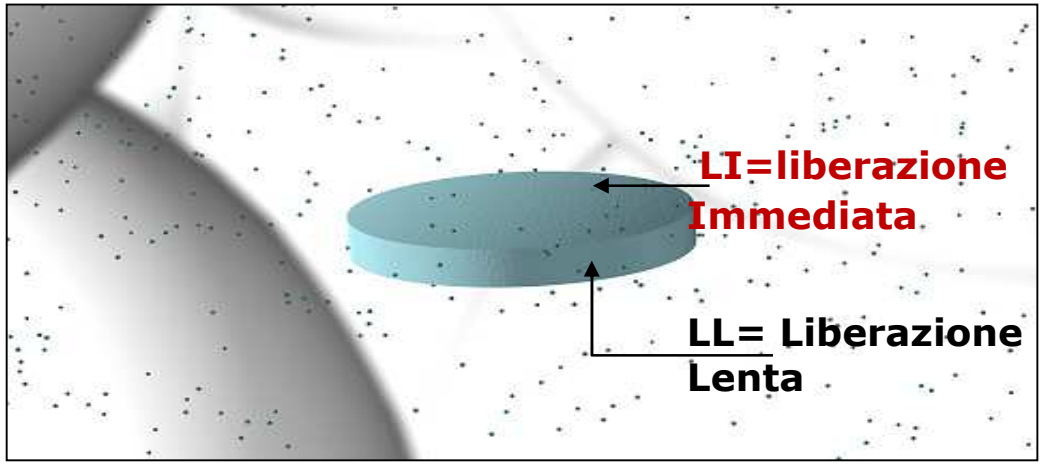
NUOVE STRATEGIE TERAPEUTICHE

Dual-release hydrocortisone preparations

Rivestimento esterno

Nucleo centrale

Ø 8 mm



Unica somministrazione giornaliera per os la mattina al risveglio

La compressa non è divisibile e non deve subire alterazioni chimico-fisiche

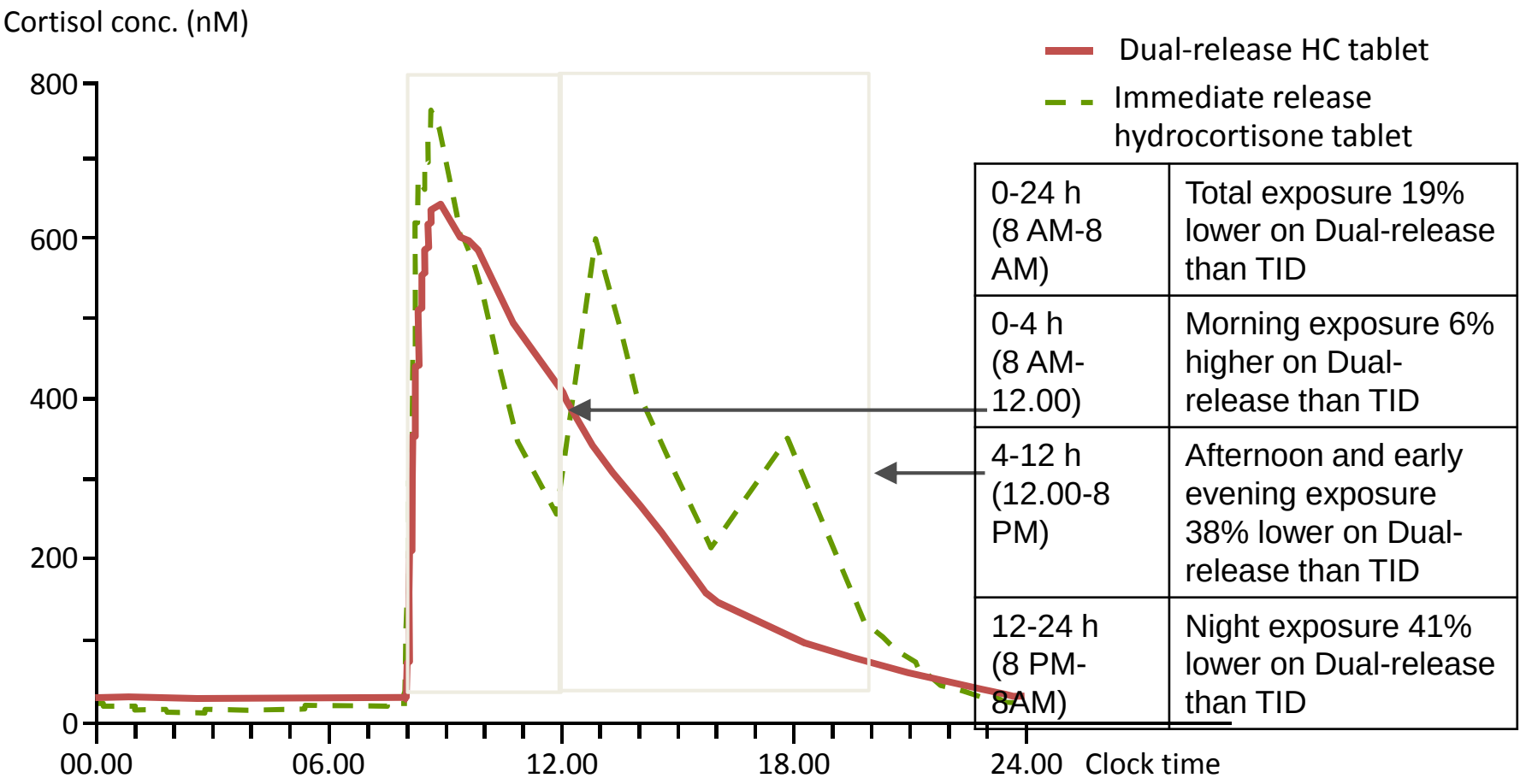
Dose di mantenimento 20-30 mg

Dosaggio inferiore in pz con una minima quota di cortisolo endogeno

40 mg dose massima studiata

G. Johannsson et al 2012
A.Falorni et al 2013

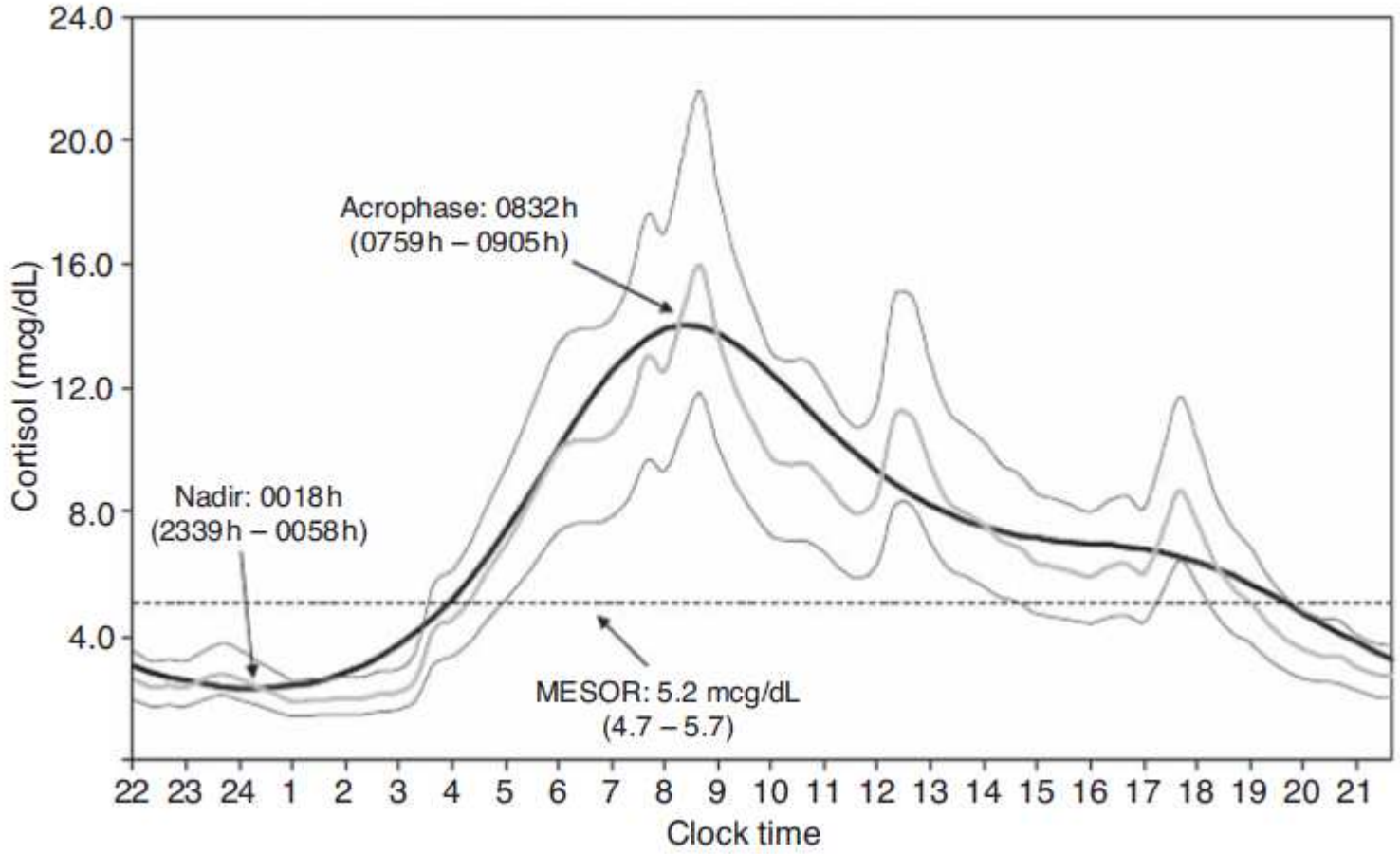
Improved Serum Cortisol Profile with Dual-Release HC tablet



0-24 h (8 AM-8 AM)	Total exposure 19% lower on Dual-release than TID
0-4 h (8 AM-12.00)	Morning exposure 6% higher on Dual-release than TID
4-12 h (12.00-8 PM)	Afternoon and early evening exposure 38% lower on Dual-release than TID
12-24 h (8 PM-8AM)	Night exposure 41% lower on Dual-release than TID

Johannsson G et al. *J Clin Endocrinol Metab* 2012;97:473–481

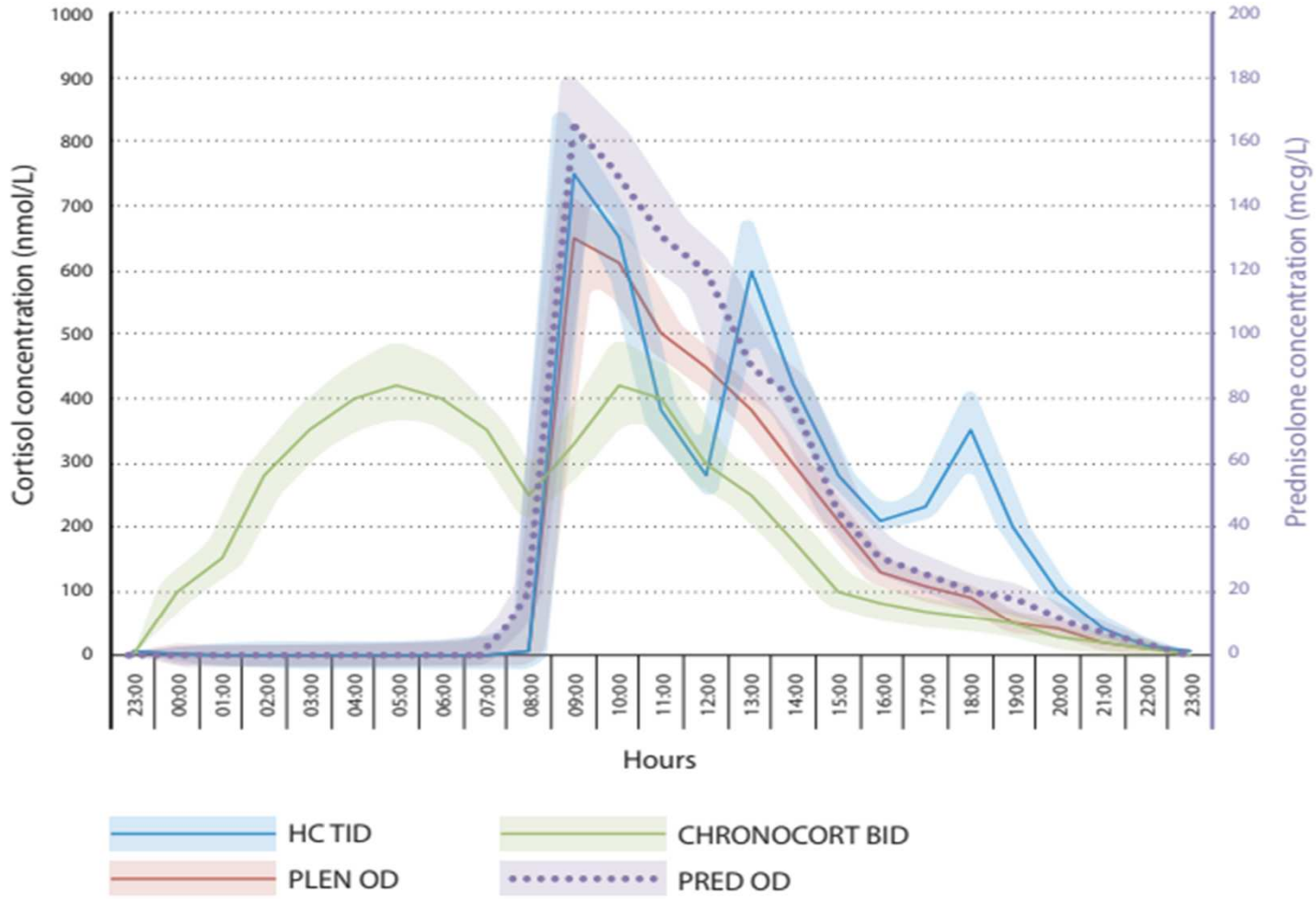
Circadian rhythm of cortisol



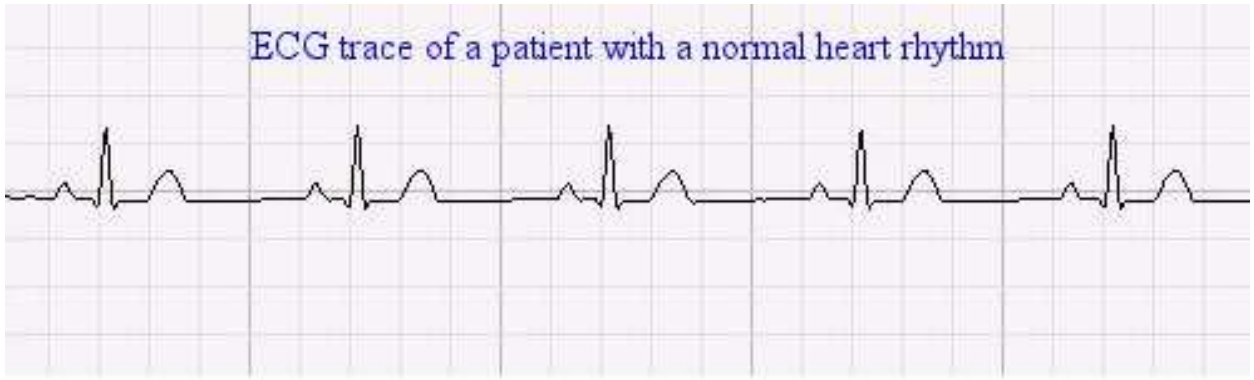
Circadian rhythm of cortisol in 33 individuals with 20-minute cortisol profiling

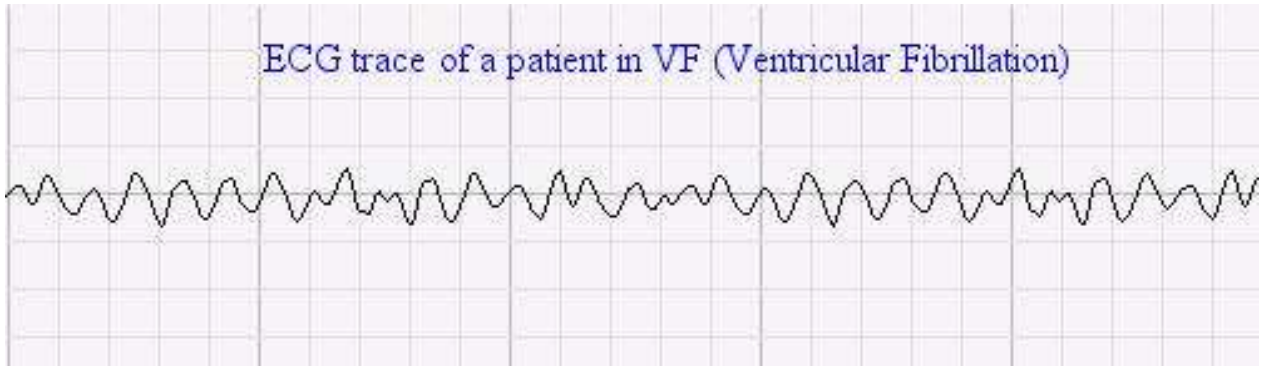
Chan S & De Bono M. Replication of cortisol circadian rhythm: new advances in hydrocortisone replacement therapyTher Adv Endocrinol Metab(2010) 1(3)

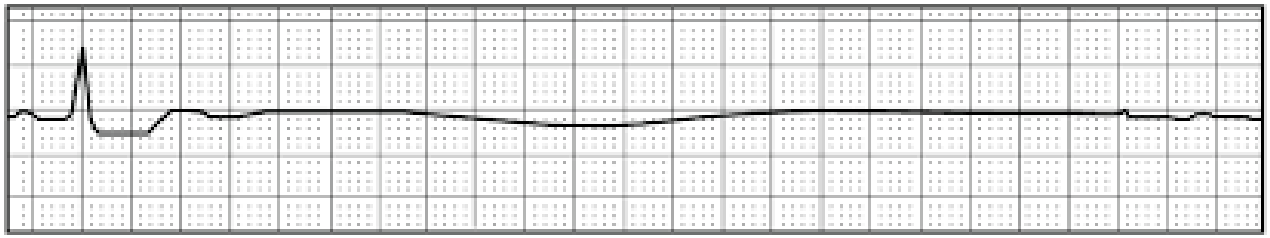
TOWARD THE TAILORING OF GLUCOCORTICOID REPLACEMENT IN ADRENAL INSUFFICIENCY: THE ITALIAN SOCIETY OF ENDOCRINOLOGY EXPERT OPINION



Il ritmo distingue gli esseri animati



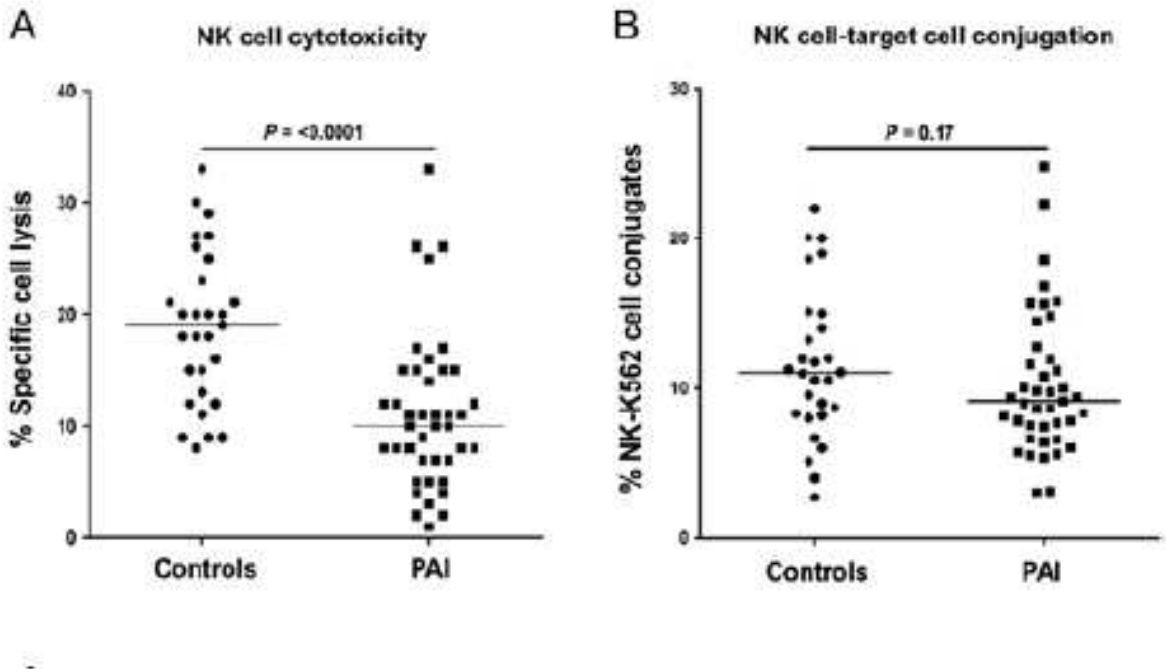




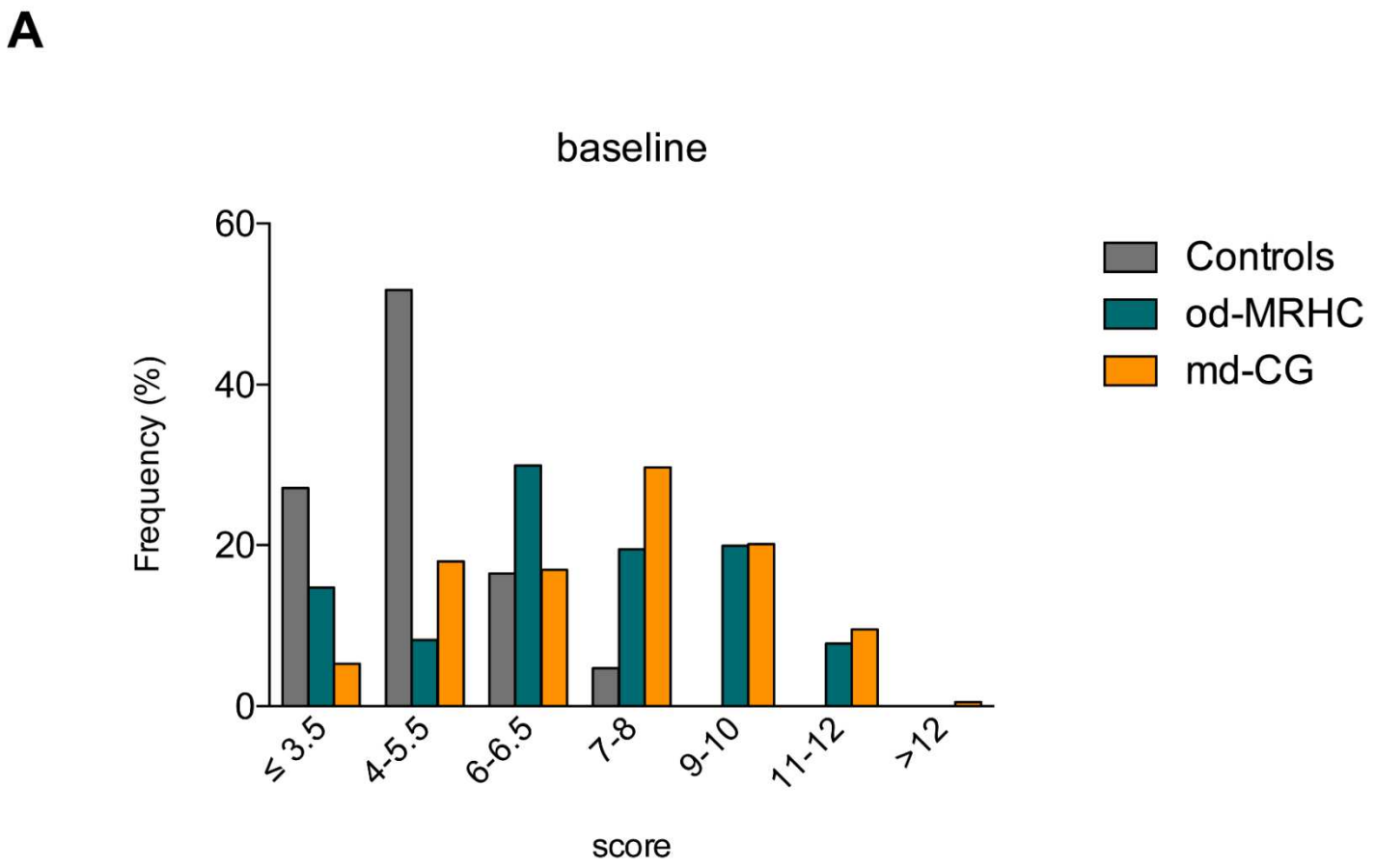
Primary adrenal insufficiency is associated with impaired natural killer cell function: a potential link to increased mortality

Irina Bancos[1,2,*], **Jon Hazeldine**[3,4,*], **Vasileios Chortis**[1,5], **Peter Hampson**[3,4], **Angela E Taylor**[1,5], **Janet M Lord**[3,4] and **Wiebke Arlt**[1,5]

European Journal of Endocrinology (2017) **176**, 471–480



Frequenza eventi infettivi minori



Isidori - Venneri et al. *The Lancet. Diabetes & Endocrinology*, 2017

The DREAM trial - NCT02277587

Dual RElease Hydrocortisone Versus conventionAl Glucocorticoid replaceMent Therapy in Hypocortisolism

MCEL: molecular and cellular endocrinology lab,
[1]Sapienza University of Rome, Rome, Italy
[2]Università Federico II, Naples, Italy

Spontaneous non-sponsored trial

Isidori et al. *Lancet Diabetes Endocrinol*. 2018 Mar;6(3):173-185.

AI6

Effect of once-daily, modified-release hydrocortisone versus standard glucocorticoid therapy on metabolism and innate immunity in patients with adrenal insufficiency (DREAM): a single-blind, randomised controlled trial

Andrea M Isidori, Mary Anna Venneri*, Chiara Graziadio, Chiara Simeoli, Daniela Fiore, Valeria Hasenmajer, Emilia Sbardella, Daniele Gianfrilli, Carlotta Pozza, Patrizio Pasqualetti, Stefania Morrone, Angela Santoni, Fabio Naro, Annamaria Colao, Rosario Pivonello, Andrea Lenzi*

Summary

Background Conventional treatment of patients with adrenal insufficiency involves administration of glucocorticoids multiple times a day and has been associated with weight gain and metabolic impairment. The optimal glucocorticoid replacement therapy for these patients is highly debated because of the scarcity of evidence from randomised trials. We aimed to establish whether the timing and pharmacokinetics of glucocorticoid replacement therapy affect the metabolism and immune system of patients with adrenal insufficiency.

Methods We did a single-blind randomised controlled trial at two reference university hospitals in Italy. Eligible patients (aged 18–80 years) with adrenal insufficiency were on conventional glucocorticoid therapy and had been stable for at least 3 months before enrolment. Patients were randomly assigned (1:1) with a computer-generated random sequence stratified by type of adrenal insufficiency and BMI to continue conventional glucocorticoid therapy

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*Contributed equally

Department of Experimental Medicine (Prof A M Isidori PhD)

Turning back the clock on adrenal insufficiency

Glucocorticoids are steroid hormones involved in the regulation of metabolism, vascular function, and brain function. Glucocorticoids also have important regulatory functions in the immune system. Therefore, synthetic glucocorticoids have been used for decades to suppress the immune response in various inflammatory disorders. The main glucocorticoid in human beings is cortisol, which is secreted from the adrenal cortex under the regulation of the hypothalamic–pituitary–adrenal axis.

Mortality and morbidity among patients with primary adrenal insufficiency (Addison's disease) was considered to be normal for decades after hydrocortisone became available. However, studies[1] have shown the risk of mortality to be increased more than twice in various subgroups of patients with adrenal insufficiency, mainly due to cardiovascular and infectious diseases. Patients with primary adrenal insufficiency have not consistently

In the DREAM study, Andrea Isidori and colleagues[7] investigate the effect of circadian exposure to cortisol in patients with primary (n=44) or secondary (n=45) adrenal insufficiency over 24 weeks. A previous study[8] showed that switching from conventional hydrocortisone three times a day to once-daily, modified-release hydrocortisone improved metabolic outcomes.[8] The DREAM trial[7] took this concept further by investigating the effect on immune function, in addition to assessing metabolic outcomes. The primary endpoint of the study was met; the authors observed that the change in bodyweight was significantly different between the treatment groups after adjustment for covariates (–4·0 kg, 95% CI –6·9 to –1·1; p=0·008). The metabolic response tended to be greater in patients with secondary adrenal insufficiency than in those with primary adrenal insufficiency.

The novel finding from this study is the effect of

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NEWS & VIEWS

ADRENAL DISEASE

Imitating the cortisol profile improves the immune system

Lisa Müller and Marcus Quinkler

A once-daily, modified-release hydrocortisone medication reduces BMI and improves glucose metabolism compared with the twice- or thrice-daily standard hydrocortisone treatment in patients with adrenal insufficiency. Now, further evidence emerges that changing to a once-daily, modified-release hydrocortisone medication improves the immune cell profile and results in fewer infections.

Refers to Isidori, A.M. et al. Effect of once-daily, modified-release hydrocortisone versus standard glucocorticoid therapy on metabolism and innate immunity in patients with adrenal insufficiency (DREAM): a single-blind, randomised controlled trial. *Lancet Diabetes Endocrinol*. https://doi.org/10.1016/S2213-

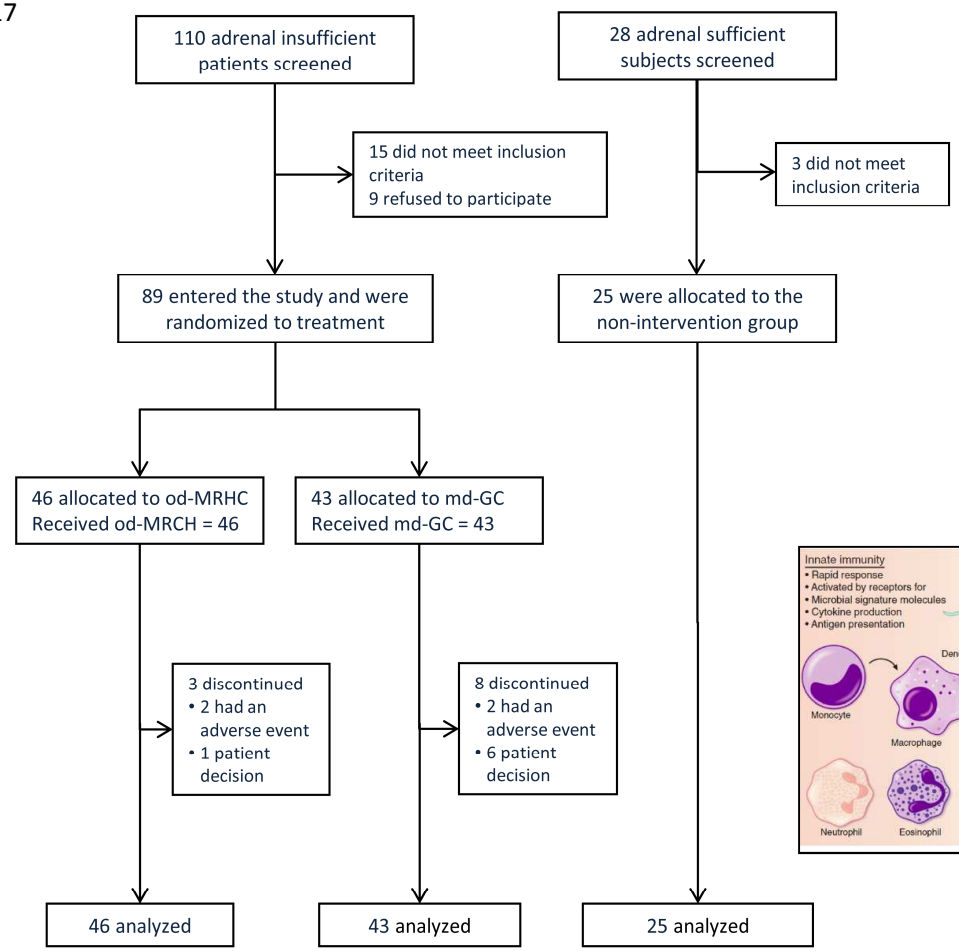
cortisol profile of the commonly used twice- or thrice-daily standard hydrocortisone replacement therapy. Changes in the immune system of patients with adrenal insufficiency were recently reported, showing reduced natural killer cell cytotoxicity[5]; however, the underlying causes were not found. The only other data on immune function in patients with adrenal insufficiency are from studies investigating dehydroepiandrosterone (DHEA) replacement, which seemed to have a positive effect on regulatory T cell levels and *FOXP3* expression in ten patients with primary adrenal insufficiency[7]. However, another study did not find a different natural killer cell cytotoxicity due to DHEA replacement[5].

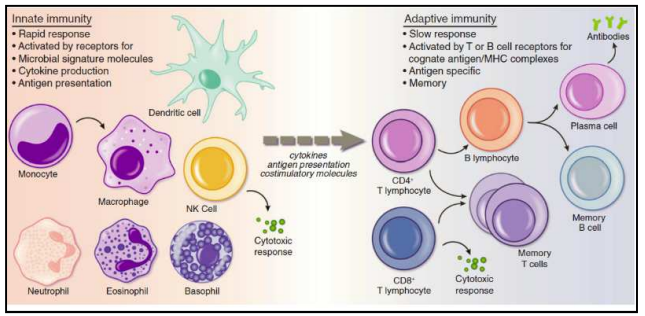
It is common knowledge that the regularly used twice- or thrice-daily standard hydrocortisone replacement therapy is non-physiological, but this is rarely recognized in daily endocrinology practice owing to the lack of alterna-

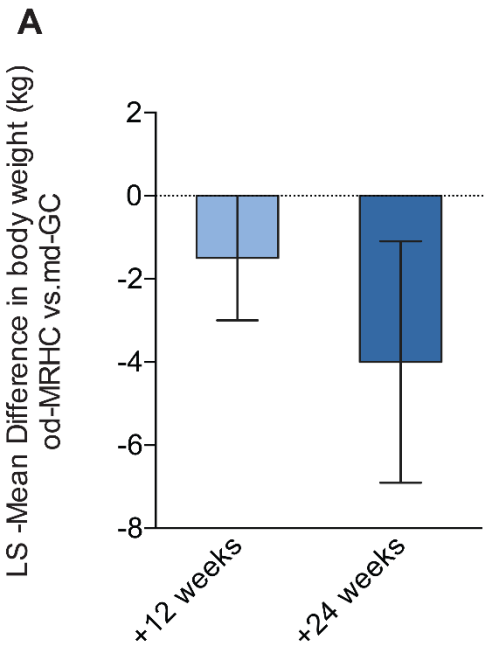
Diapositiva 26

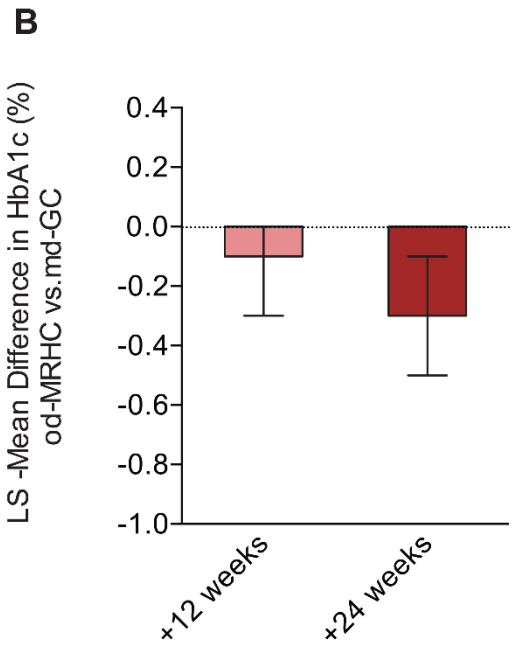
AI6 Quando metti le slided con i titoli.: le affiliazioni non servono! mentre serve l'anno di publicazione e il numero..... di quand'è è roba recente? e anche la rivista manca. questo per tutte le slides. ogni slides deve avere sotto ..... per esempio Shimba et al, Nature Immunology. 2015: 46:357.... (ovviamente sono dati messi a caso)....
Andrea Isidori; 12/05/2018

Isidori Venneri et al. *The Lancet. Diabetes & Endocrinology*, 2017

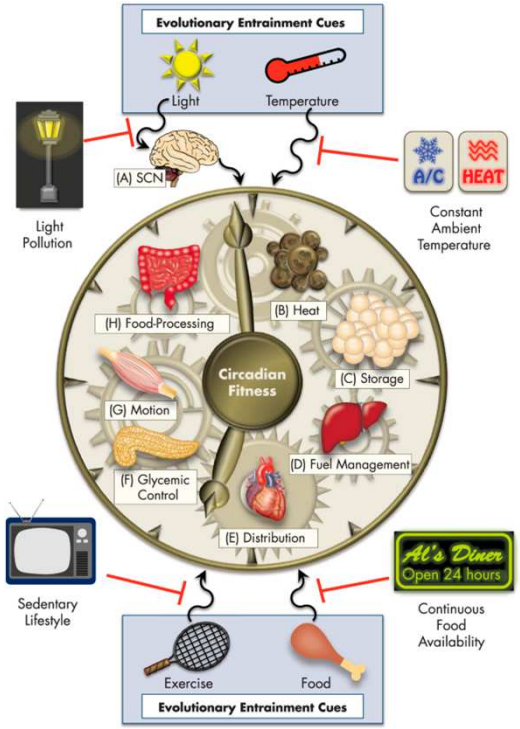








Isidori et al. *Lancet Diabetes Endocrinol*. 2018 Mar;6(3):173-185.



Endocr Rev. 2015;36(3):289-304

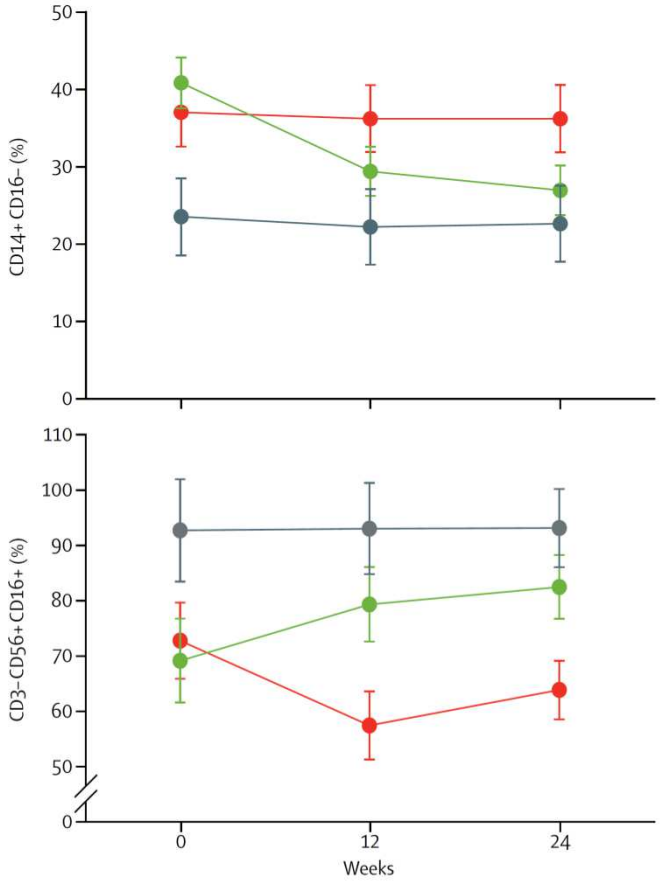
Outcome	Adrenally sufficient	Adrenally insufficient	Independent sample t–test
Number of subjects	25	89	*P* value
Circulating blood cells (mean, 95% CI)			
Neutrophils (%)[a]	58 (55 to 61)	55 (53 to 57)	.093
Cell count (n)	3510 (3196 to 3824)	4149 (3669 to 4629)	.246
Lymphocytes (%)[a]	30 (28 to 32)	34 (32 to 36)	.012
Cell count (n)	1852 (1694 to 2011)	2351 (2213 to 2490)	.034
Monocytes (%)[a]	6.6 (5.8 to 7.4)	6.5 (6.1 to 7.0)	.871
Cell count (n)	424 (373 to 474)	476 (442 to 509)	.162
Eosinophils (%)[a]	2.8 (1.7 to 3.9)	2.3 (2.0 to 2.7)	.451
Cell count (n)	182 to (102 to 262)	177 (155 to 200)	.869
Basophils (%)[a]	0.5 (0.4 to 0.7)	0.6 (0.5 to 0.7)	.590
Cell count (n)	33 to (26 to 39)	54 (37 to 71)	.240
$CD14^+CD16^-$ (%) (classical)[b]	24 (22 to 25)	37 (34 to 40)	<.001
Cell count (n)	540 (478 to 601)	1052 (947 to 1157)	<.001
$CD14^+CD16^+$ (%) (non-classical)[b]	3.6 (3.1 to 4.0)	4.1 (3.6 to 4.6)	.157
Cell count (n)	82 (69 to 95)	112 (98 to 126)	.002
$CD16^+CD14^-$ (%)[b]	11 (10 to 12)	4.8 (3.9 to 5.7)	<.001
Cell count (n)	250 (213 to 288)	130 (107 to 153)	<.001
$CD16^+$NK ($CD3^-CD56^+CD16^+$) (%)[b]	94 (92 to 95)	71 (65 to 76)	<.001
Cell count (n)	228 (201 to 254)	128 (107 to 149)	<.001
$CD3^+$ (%)[b]	54 (52 to 56)	54 (51 to 57)	.818
Cell count (n)	1212 (1122 to 1302)	1540 (1403 to 1677)	<.001
$CD19^+$ (%)[b]	8.8 (7.9 to 9.8)	9.6 (8.6 to 10.6)	.247
Cell count (n)	199 (179 to 219)	281 (240 to 322)	.001

Isidori et al. *Lancet Diabetes Endocrinol*. 2018 Mar;6(3):173-185.

Shift timing of GC replacement affect circulating monocytes and NK cells in AI patients

Calssical (inflammatory) Monocytes

% of CD16⁺ NK cells



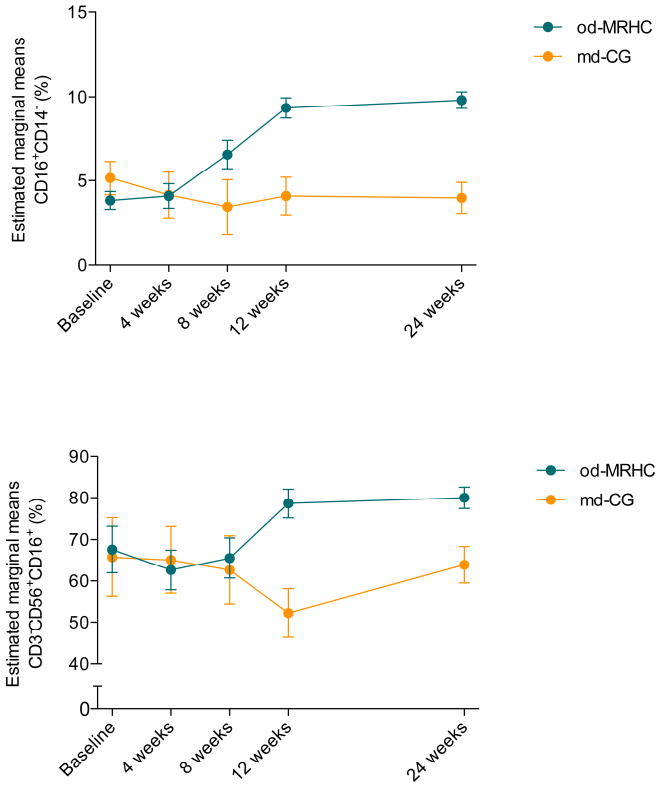
Once-daily

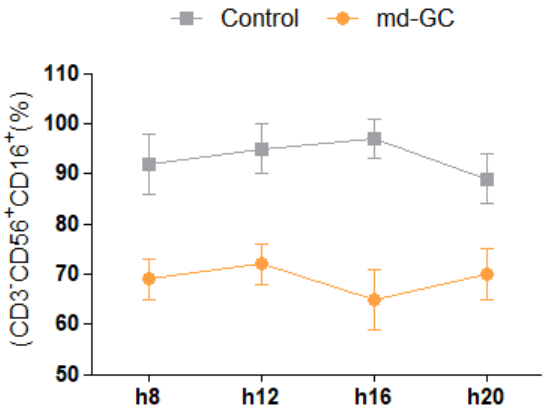
Controls
Switch treatment group
Standard treatment group

Multiple-daily

Isidori et al. *Lancet Diabetes Endocrinol*. 2018 Mar;6(3):173-185.

Time courses of NK cells exclude cell recirculation



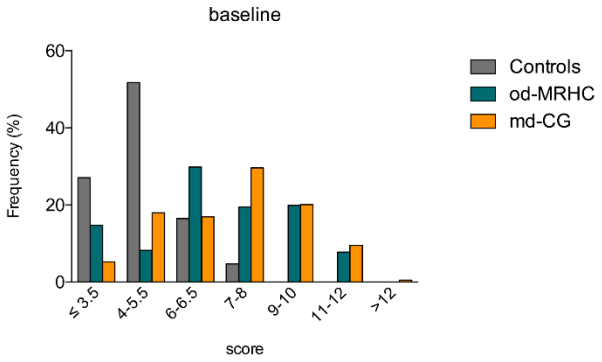


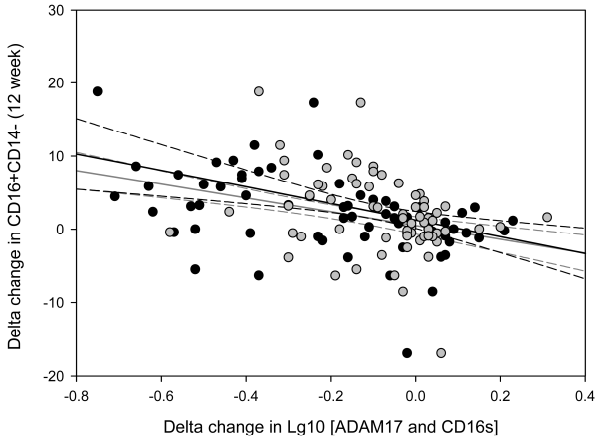
Isidori unpublished results

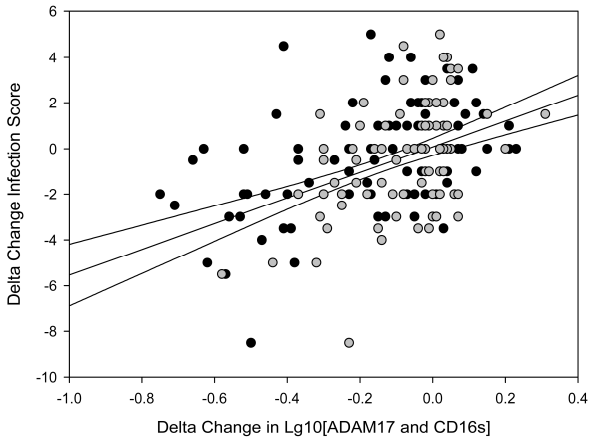
Isidori - Venneri et al. *The Lancet. Diabetes & Endocrinology*, 2017

Correlation between immune changes and infection score

A

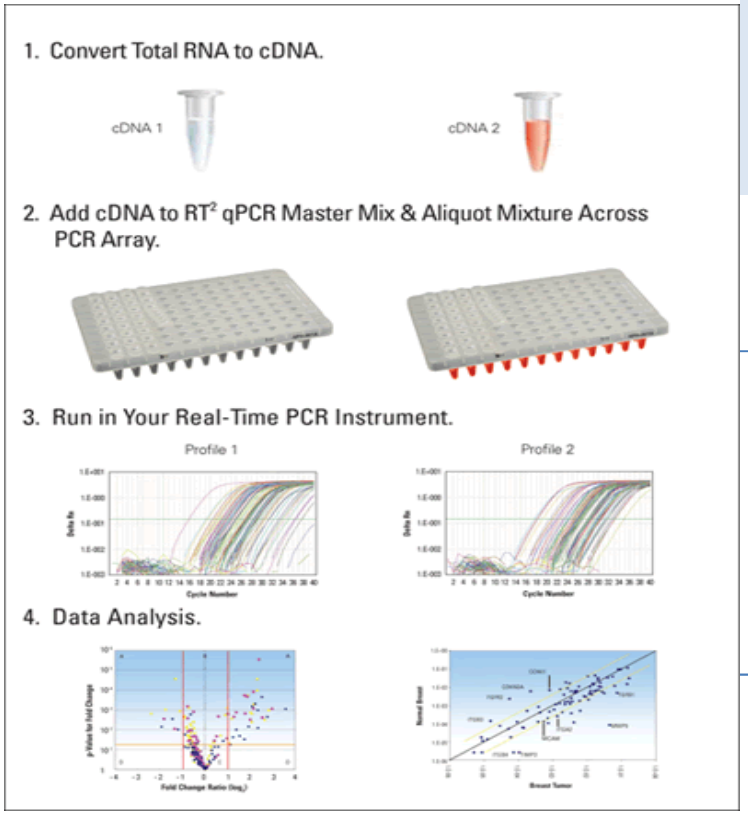






Isidori - Venneri et al. *The Lancet. Diabetes & Endocrinology*, 2017

Circadian Rhythm of Glucocorticoid Administration Entrains Clock Genes in Immune Cells: A DREAM Trial Ancillary Study

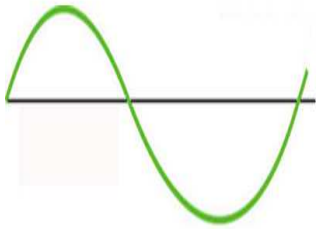


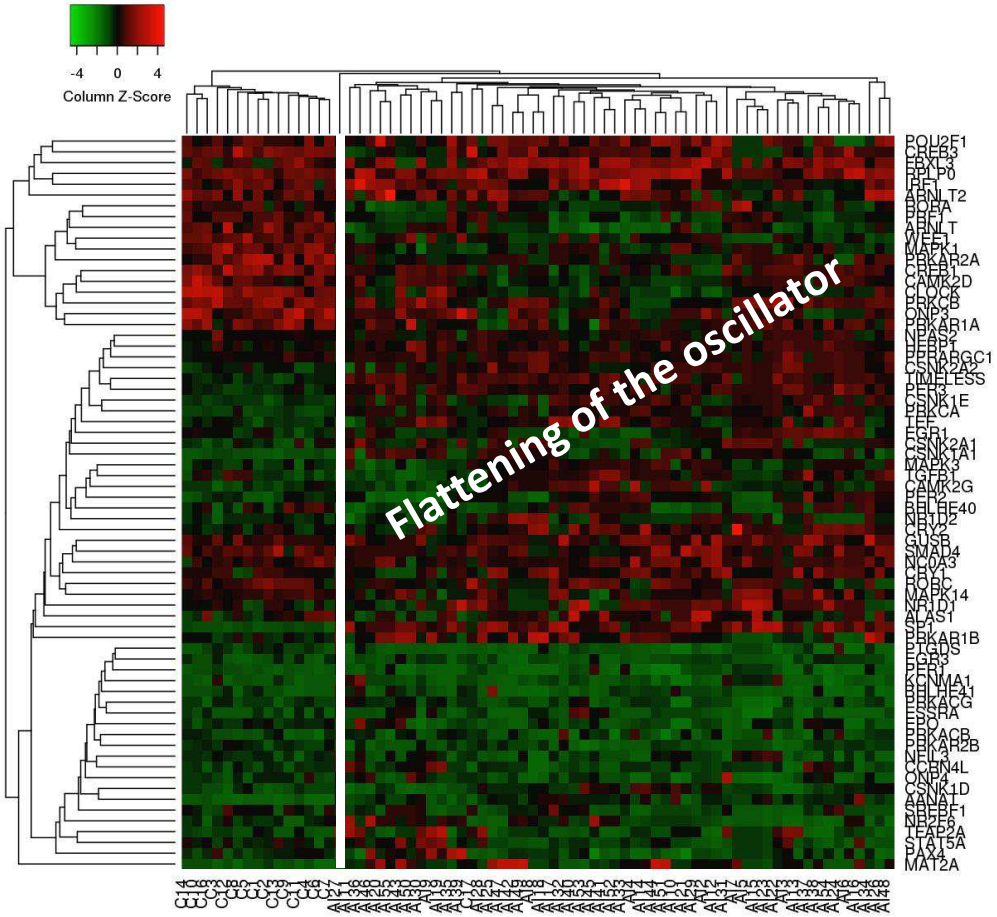
PCR amplification in Real time PCR array predesigned 96-well panel for use with SYBR® Green Circadian rhythms (SAB Target List) H96

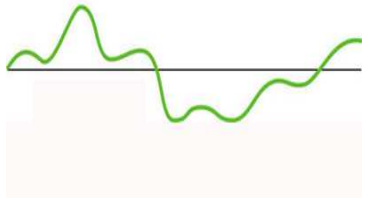
Pooled patients by treatment group → Sorted by cell type:
- Lympho
- Mono

Individually analysed Patients → Total PBMCs

Heat map of the transcriptome at baseline

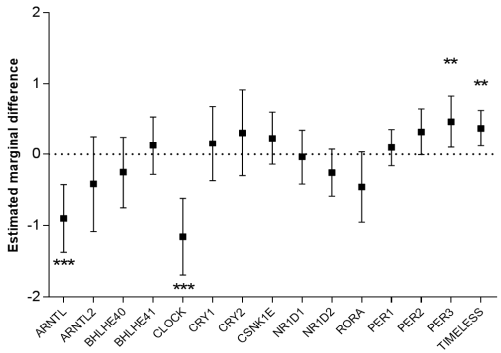




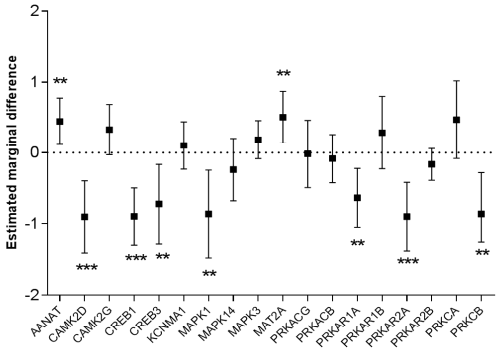


19 genes displayed a statistically different level of expression in PBMCs drawn from healthy vs AI subjects

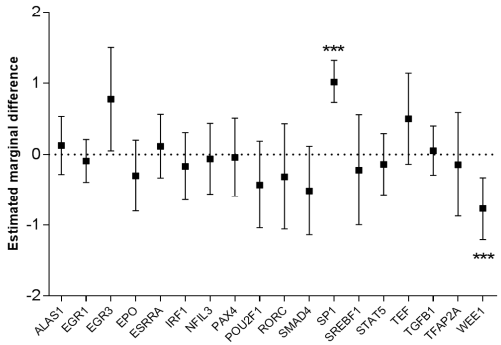
Clock gene group



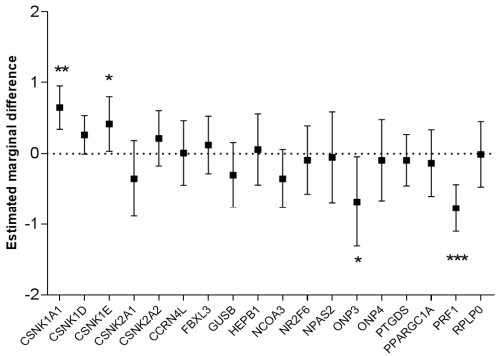
CREB signaling gene group



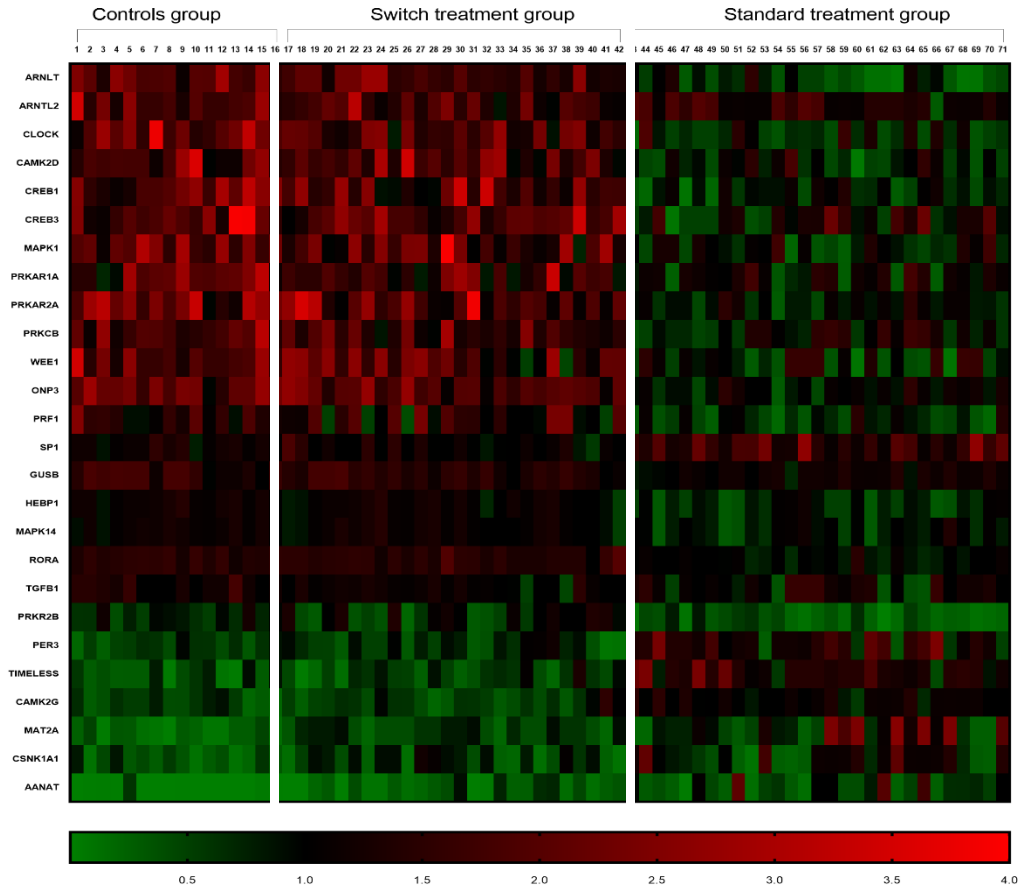
C **Transcription** gene group



D Other **Circadian Related**



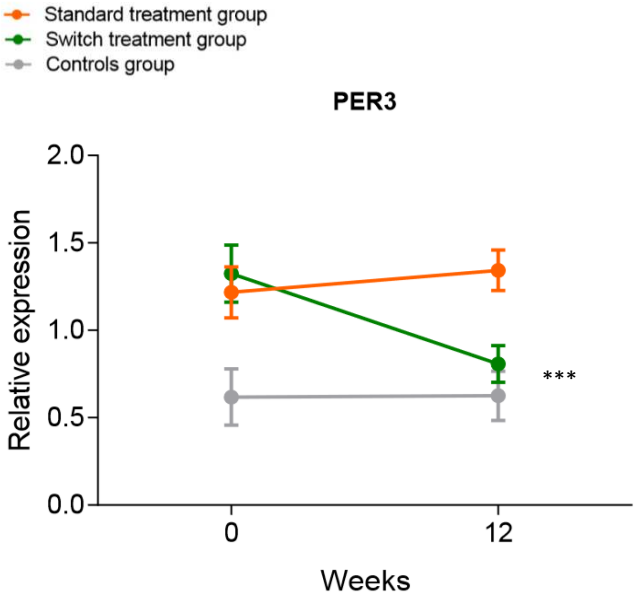
Impact of switching glucocorticoids replacement therapy



12-weeks post treatment switch:

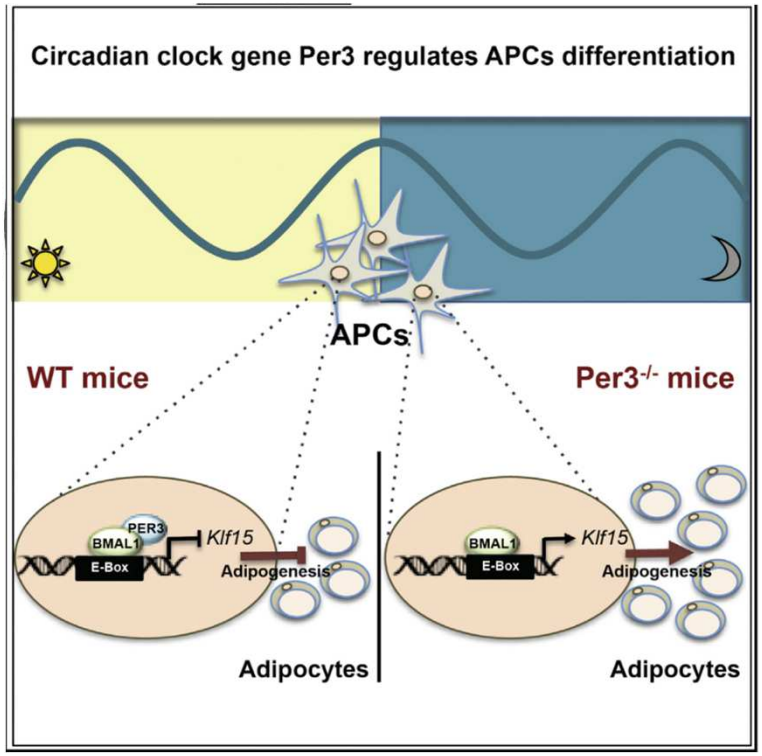
multiple → once daily glucocorticoid administration

Differentially modulated genes in all groups at baseline and after treatment

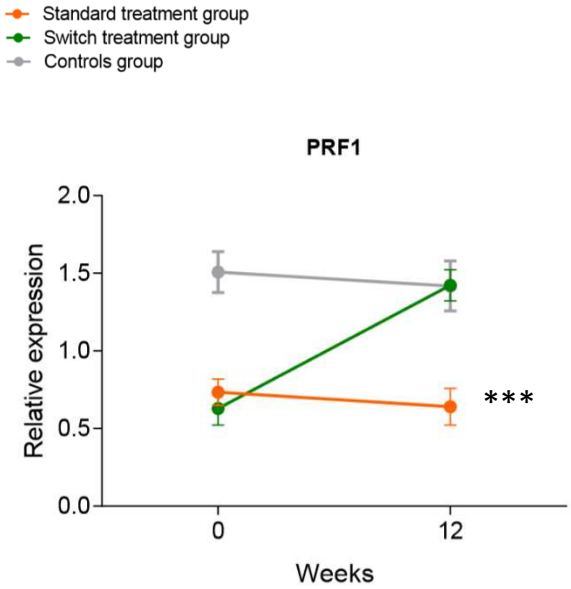


PER3 plays an interesting role in adipogenesis homeostasis by regulating Klf15, a pivotal gene in adipocyte differentiation.

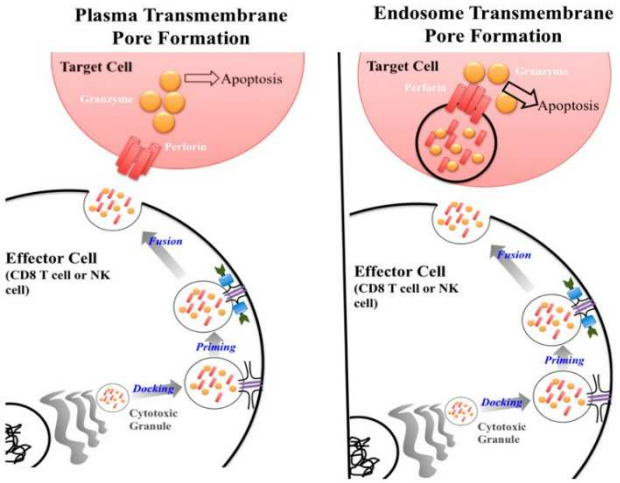
Aggarwal et al *Cell Rep*. 2017



Differentially modulated genes in all groups at baseline and after treatment

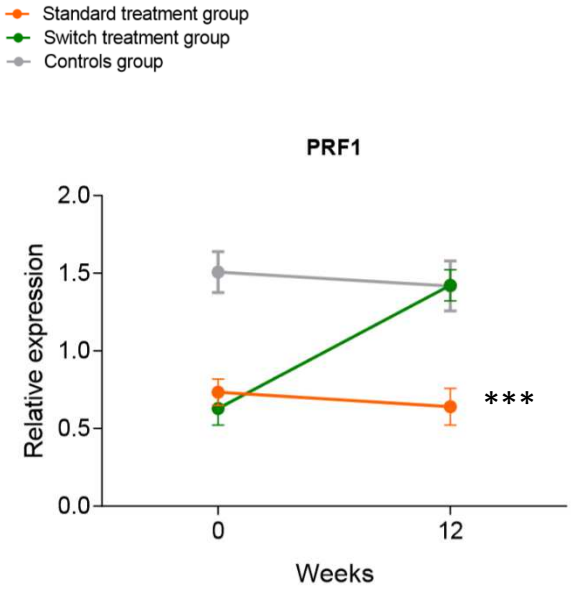


PRF1 deficiency -> IMMUNE DEFECT



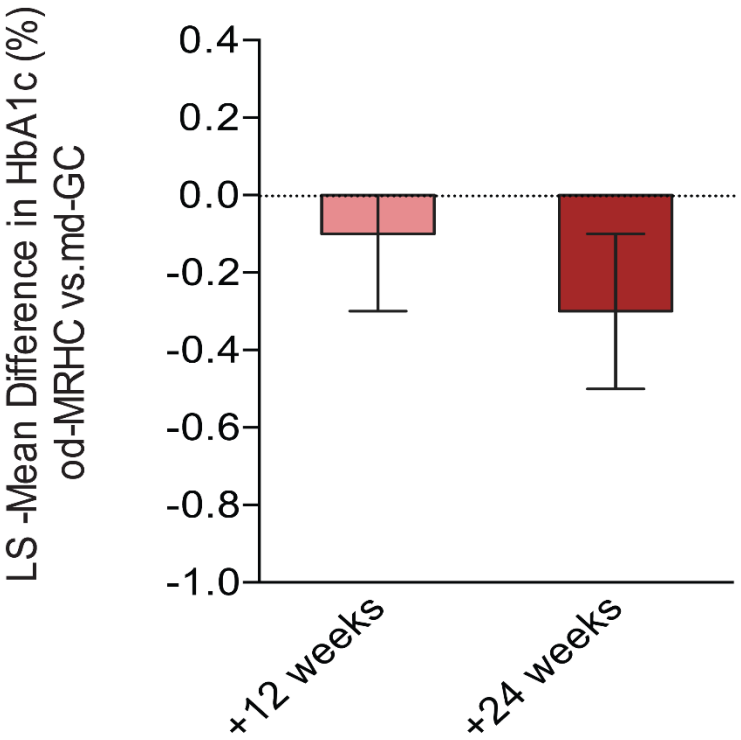
Perforin forms membrane pores that allow the release of granzymes and subsequent cytolysis of target cells.

Differentially modulated genes in all groups at baseline and after treatment

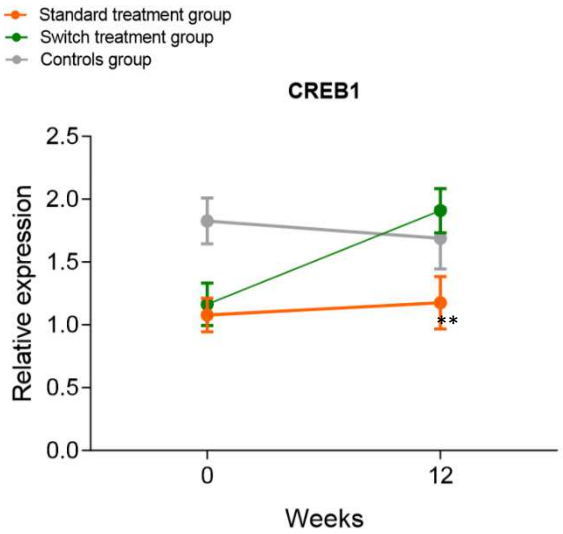


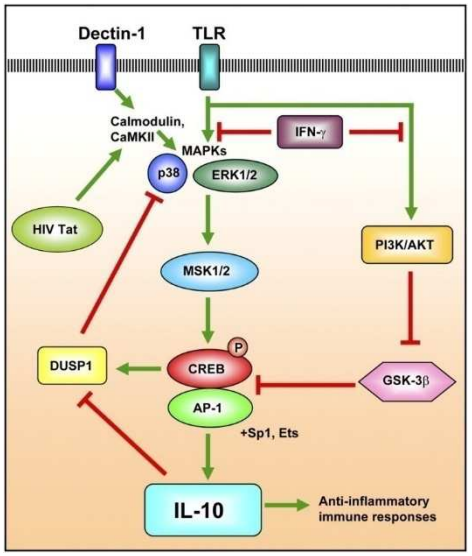
↓ **PRF1 → Adipose Tissue Inflammation**

↑ **PER3 → Impaired Adipogenesis**



Differentially modulated genes in all groups at baseline and after treatment





CREB is induced by a variety of growth factors and inflammatory signals; it can promote **anti-inflammatory immune responses**, through inhibition of NF-kB, induction of IL-10, but it is also considered a **nutrient-sensing transcriptional regulatory proteins** (with FOXO-p300, PGC-1, and SP1 family members).

Wen A e al. J Immunol 2010

Circadian Rhythm of Glucocorticoid Administration Entrains Clock Genes in Immune Cells: A DREAM Trial Ancillary Study

Mary Anna Venneri,[1]* Valeria Hasenmajer,[1]* Daniela Fiore,[1] Emilia Sbardella,[1] Riccardo Pofi,[1,2] Chiara Graziadio,[1] Daniele Gianfrilli,[1] Claudia Pivonello,[3] Mariarosaria Negri,[3] Fabio Naro,[4] Ashley B. Grossman,[2,5] Andrea Lenzi,[1] Rosario Pivonello,[3] and Andrea M. Isidori[1]

J Clin Endocrinol Metab, August 2018, 103(8):2998–3009

Resetting the expression (↑↓) of 9.00 AM clock-related genes correlates with the improvement in clinical outcomes (metabolism, inflammation, infections).

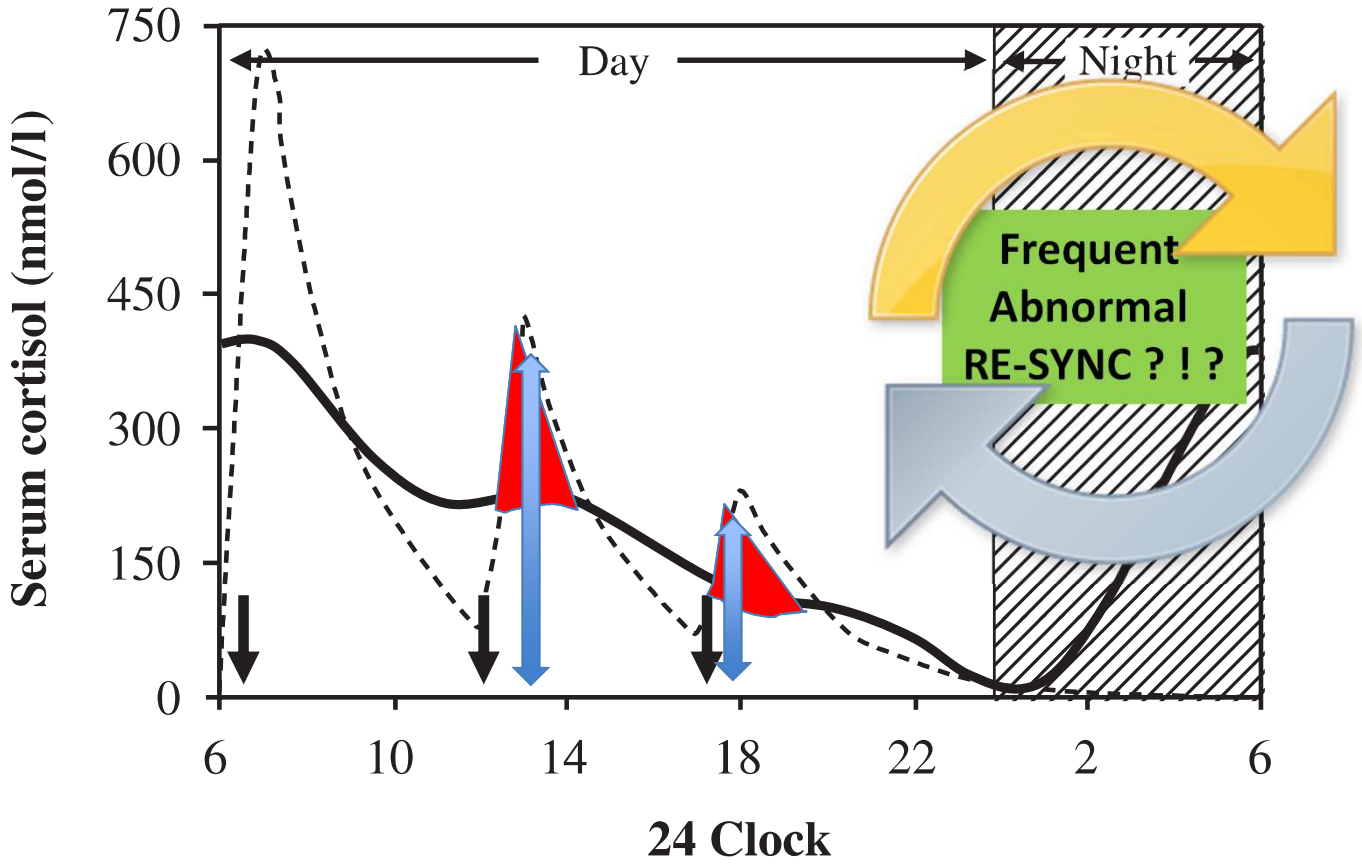
Table 3. Delta Change Correlation Matrix

Gene		Δ-BMI	Δ-HbA1c	Δ-High-Density Lipoprotein	Δ-TG[a]	Δ-SBP[b]	Δ-DBP[c]	Δ-CD16$^+$ CD14$^-$ Cells	Δ-CD14$^+$ CD16$^-$ Cells	Δ-CD16$^+$ NK Cells	Δ-ADAM17[d]	Δ-CD16s[d]	Δ-Infections[e]
Δ-*AANAT*	*r*	−0.272	0.394[f]	0.176	−0.096	−0.092	0.183	−0.016	−0.009	0.008	0.197	0.359	−0.185
	P	0.132	**0.038**	0.352	0.603	0.617	0.315	0.929	0.963	0.970	0.393	0.110	0.303
Δ-*ARNTL*	*r*	−0.279	0.023	0.023	−0.091	0.184	−0.136	0.171	−0.166	−0.011	−0.398	−0.252	−0.252
	P	0.122	0.909	0.905	0.620	0.314	0.457	0.349	0.364	0.958	0.074	0.270	0.157
Δ-*ARNTL2*	*r*	−0.294	−0.071	−0.039	−0.222	−0.055	0.495[g]	0.060	−0.041	0.038	−0.493[f]	−0.352	−0.182
	P	0.109	0.724	0.840	0.230	0.768	**0.005**	0.749	0.826	0.857	**0.023**	0.118	0.318
Δ-*CAMK2D*	*r*	0.186	−0.384[f]	−0.209	0.003	0.271	−0.178	0.234	−0.400[f]	0.232	−0.615[g]	−0.378	−0.053
	P	0.317	**0.048**	0.276	0.985	0.141	0.339	0.205	**0.026**	0.265	**0.004**	0.100	0.775
Δ-*CLOCK*	*r*	−0.094	−0.088	0.017	0.017	0.334	−0.008	0.255	−0.196	0.062	−0.360	−0.253	−0.246
	P	0.609	0.657	0.927	0.927	0.061	0.966	0.159	0.282	0.764	0.109	0.268	0.167
Δ-*CREB1*	*r*	0.067	−0.165	−0.098	0.021	0.364[f]	−0.300	0.135	−0.119	−0.081	−0.191	−0.092	−0.003
	P	0.715	0.403	0.607	0.907	**0.040**	0.095	0.462	0.518	0.695	0.407	0.690	0.986
Δ-*CREB3*	*r*	0.075	−0.200	−0.034	−0.180	0.060	−0.026	0.272	−0.082	0.189	−0.343	−0.303	−0.056
	P	0.683	0.298	0.857	0.325	0.746	0.889	0.133	0.655	0.345	0.118	0.170	0.757
Δ-*CSNK1A1*	*r*	−0.366[f]	0.507[g]	0.254	0.092	−0.110	0.199	−0.148	0.343	−0.197	0.585[g]	0.414	−0.108
	P	**0.040**	**0.006**	0.175	0.615	0.549	0.276	0.418	0.055	0.335	**0.005**	0.062	0.550
Δ-*CSNK1E*	*r*	0.018	0.258	−0.223	0.344	−0.082	0.137	0.139	−0.080	0.062	0.104	0.081	0.244
	P	0.924	0.177	0.229	0.054	0.657	0.453	0.449	0.665	0.759	0.646	0.720	0.171
Δ-*GUSB*	*r*	−0.335	0.014	−0.041	−0.216	−0.112	−0.251	0.358[f]	−0.310	0.275	−0.685[g]	−0.565[g]	−0.402*
	P	0.061	0.943	0.831	0.236	0.540	0.165	**0.044**	0.084	0.173	**0.001**	**0.008**	**0.020**
Δ-*MAPK1*	*r*	−0.021	−0.293	−0.028	−0.161	0.184	−0.001	0.177	−0.219	0.078	−0.566[g]	−0.449[f]	−0.143
	P	0.910	0.137	0.884	0.388	0.323	0.996	0.342	0.235	0.712	**0.009**	**0.047**	0.435
Δ-*MAT2A*	*r*	−0.255	0.439[f]	0.222	−0.051	0.081	−0.024	−0.032	0.072	−0.068	0.195	0.326	−0.098
	P	0.158	**0.019**	0.238	0.780	0.661	0.894	0.860	0.694	0.742	0.396	0.149	0.586
Δ-*ONP3*	*r*	0.257	−0.352	−0.222	−0.002	0.041	0.059	0.581[g]	−0.355[f]	0.312	−0.527[f]	−0.475[f]	−0.306
	P	0.162	0.066	0.237	0.991	0.826	0.752	**0.001**	**0.050**	0.121	**0.012**	**0.025**	0.089
Δ-*PER3*	*r*	0.070	0.325	0.125	−0.019	0.289	−0.315	−0.280	0.327	−0.175	0.505[f]	0.443[f]	0.433[f]
	P	0.698	0.085	0.504	0.918	0.103	0.074	0.115	0.063	0.394	**0.017**	**0.039**	**0.010**
Δ-*PRF1*	*r*	0.093	−0.446[f]	−0.268	−0.046	−0.042	0.044	0.489[g]	−0.437[f]	0.442[f]	−0.697[g]	−0.691[g]	−0.309
	P	0.612	**0.017**	0.153	0.803	0.821	0.812	**0.004**	**0.012**	**0.024**	**<0.001**	**0.001**	0.080
Δ-*PRKAR1A*	*r*	0.011	−0.239	−0.005	−0.168	0.223	0.175	0.313	−0.288	0.137	−0.427	−0.357	−0.187
	P	0.952	0.220	0.977	0.358	0.219	0.337	0.081	0.110	0.503	0.054	0.112	0.297
Δ-*PRKAR2A*	*r*	−0.189	−0.163	−0.041	0.084	0.035	0.123	0.363[f]	−0.308	0.143	−0.592[g]	−0.420	−0.465[g]
	P	0.318	0.426	0.838	0.660	0.856	0.518	**0.049**	0.098	0.507	**0.008**	0.073	**0.008**
Δ-*PRKCB*	*r*	−0.111	0.108	0.266	0.262	0.185	0.114	0.202	−0.245	0.156	0.025	0.302	0.177
	P	0.457	0.500	0.084	0.082	0.213	0.447	0.269	0.177	0.446	0.885	0.077	0.233
Δ-*RORA*	*r*	−0.252	−0.069	0.009	−0.092	0.099	0.088	0.100	−0.199	0.088	−0.504[f]	−0.358	−0.243
	P	0.163	0.728	0.961	0.615	0.590	0.631	0.587	0.275	0.670	**0.020**	0.111	0.172
Δ-*SP1*	*r*	−0.017	0.236	0.214	−0.305	0.063	0.015	−0.323	0.350	−0.093	0.462[f]	0.659[g]	0.307
	P	0.929	0.226	0.257	0.095	0.738	0.935	0.076	0.053	0.650	**0.031**	**0.001**	0.087
Δ-*TIMELESS*	*r*	0.183	0.210	0.057	0.103	0.377[f]	−0.329	−0.181	0.303	−0.186	0.587[g]	0.736[g]	0.408[g]
	P	0.317	0.284	0.764	0.574	**0.034**	0.066	0.321	0.092	0.363	**0.005**	**<0.001**	**0.019**
Δ-*WEE1*	*r*	−0.105	−0.375[f]	−0.144	0.180	−0.011	−0.013	0.583[g]	−0.542[g]	0.334	−0.778[g]	−0.645[g]	−0.527[g]
	P	0.553	**0.041**	0.432	0.307	0.951	0.940	**<0.001**	**0.001**	0.096	**<0.001**	**0.001**	**0.001**

Perspectives: toward better **Chronopharmacology**

Non-physiological cortisol replacement in adrenal insufficiency

Immediate release HC (TID) in patients with AI does
not mimick cortisol rhythm by giving multiple peaks and nadirs

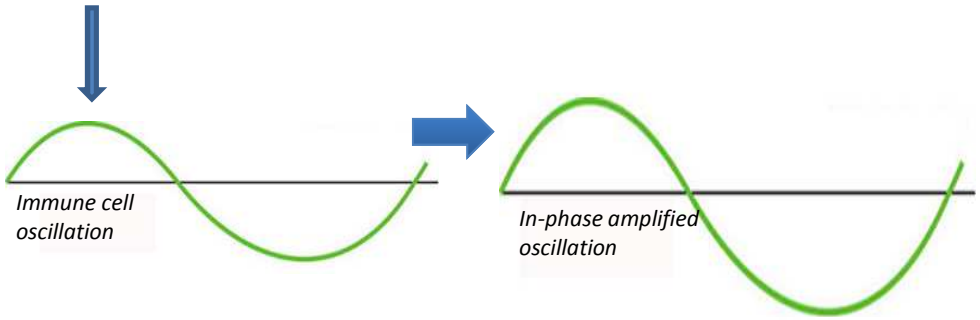


The non-physiological circadian profile rather than the dose could be the major explanation for the AI outcome

Peak M Mah *Clinical Endocrinology* 2004;61:367–375.

Fixing the broken clock?

Single Pulse GC



COMMENTARY

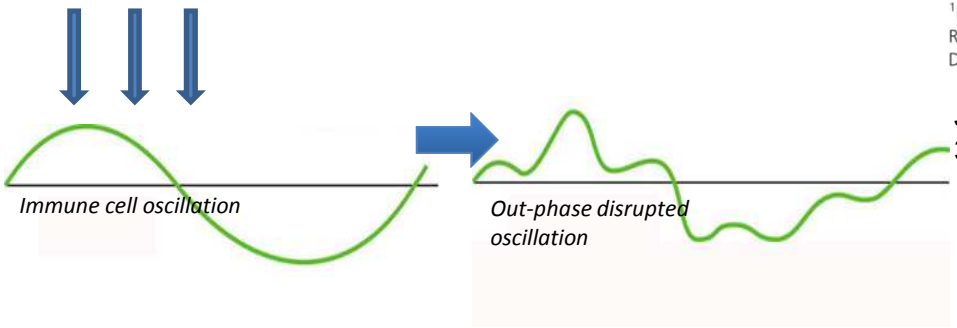
Physiological Glucocorticoid Replacement in Adrenal Insufficiency: Does It Fix the Broken Clock?

Matthew R. Brown[1] and Aleksey V. Matveyenko[1,2]

[1]Department of Physiology and Biomedical Engineering, Mayo Clinic School of Medicine, Mayo Clinic, Rochester, Minnesota 55905; and [2]Department of Medicine, Division of Endocrinology, Metabolism, Diabetes, and Nutrition, Mayo Clinic School of Medicine, Mayo Clinic, Rochester, Minnesota 55905

J Clin Endocrinol Metab, September 2018, 103(9):3511–3513

Multiple Pulses GC



COSA BISOGNA SAPERE SUL PLENADREN

Per il passaggio da terapia convenzionale a plenadren è di aiuto l'applicazione CORTICONVERTER

Nella pratica clinica il passaggio da Idrocortisone BID o TID a plenadren prevede lo stesso dosaggio

A causa della minore biodisponibilità del plenadren bisogna monitorare sempre la risposta clinica ed eventualmente personalizzare la dose

Nei pazienti affetti da Insufficienza corticosurrenalica secondaria, in trattamento con altri ormoni, ad esempio GH, la posologia del plenadren non va modificata

In presenza di IPOTIROIDISMO, iniziare prima la terapia con Plenadren e successivamente con Levotiroxina sodica

COSA BISOGNA SAPERE SUL PLENADREN

MALATTIE INTERCORRENTI

NON sottovalutare il rischio di crisi surrenalica

Raddoppiare il dosaggio di glucocorticoidi in caso di FEBBRE o di altre patologie, triplicare per temperatura corporea > 39° assumendo un'altra compressa di Plenadren dopo almeno 8 ore dalla precedente senza modificare la dose del mattino

•In alternativa somministrare compresse di Idrocortisone a rilascio immediato

In caso di vomito persistente e/o diarrea bisogna somministrare Glucocorticoidi per via i.m. o endovena

NON SOTTOVALUTARE MAI LA PRESENZA DI INFEZIONI

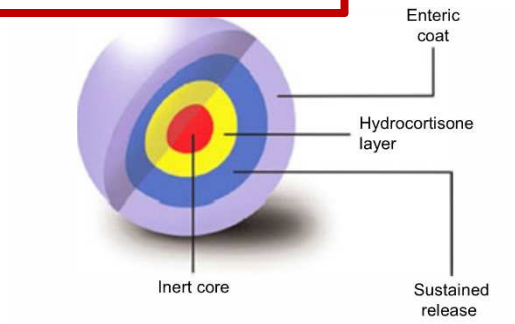
A.Falorni et al 2013
G. Johannsson 2015

Clinical situation	Standard GC		MRHC	
	Pros	**Cons**	**Pros**	**Cons**
Young patients with PAI	Readily available The dose can be finely adjusted	Potential risks from long term effects of overtreatment and reduced adherence to treatment with multiple daily doses	Time gain Better adherence to treatment Improved QoL Prevention of some metabolic and cardio-vascular comorbidities	Cost Tablets in fixed doses (5 and 20 mg)
Young patients with PAI associated with type 1 diabetes		Potential risks from long term effects of overtreatment and reduced adherence to treatment with multiple daily doses	Trials show improved HbA1C in type 1 diabetes Better adherence to treatment Improved QoL	Cost Tablets in fixed doses (5 and 20 mg)
Elderly patients with PAI	Better adherence where disease has been stable for several years Multiple doses might not be a negative point in forgetful patients, as the effect of skipping one dose is reduced		Better adherence to treatment	Elderly patients who are stable and satisfied with their treatment should not be switched to MRHC, except in the presence of specific unmet needs
SAI and other pituitary gland deficiencies treated for less than one year with GCs	The immediate release is easier to manage, considering the possibility of frequent dose adjustment and of stopping GCs in the event of recovery from the cause of AI		Time gain Better adherence to treatment Improved QoL Prevention of some metabolic and cardio-vascular comorbidities	The fixed doses of the commercially available modified-release preparations are not compatible with the low-intermediate dose and frequent dose adjustments typically needed by patients with recent-onset secondary hypopituitarism
SAI and 1 or more pituitary gland deficiencies treated for more than one year (?) with GCs		Low adherence to multiple treatment schedules	Better adherence to multiple treatment schedules	
SAI and good control with low-medium doses of GCs (e.g. a single morning dose)	Immediate release HC or CA is indicated, given the single daily dose			Not indicated due to risks associated with excessive doses
Primary, secondary AI requiring high doses of GCs (35-40 mg)	Most indicated treatment, given the lower costs			Not indicated, given the higher costs and dose-titration difficulties
Rare diseases and syndromes associated with AI, such as familial GC deficiencies, triple-A (Allgrove) syndrome and congenital adrenal hyperplasia		Not recommended, considering the comorbidities and long-term multiple treatment schedules	Better adherence to long-term multiple treatments	
Special populations (poor glycaemic control and/or intestinal absorption associated with AI)		Not recommended, considering the long-term multiple treatment schedules and absorption problems	Better long-term adherence and efficacy: propose trying MRHC	

what else?

Modified-release hydrocortisone tablet to provide circadian profile

Clinical Endocrinology (2014) **80**, 554–561 doi: 10.1111/cen.12316



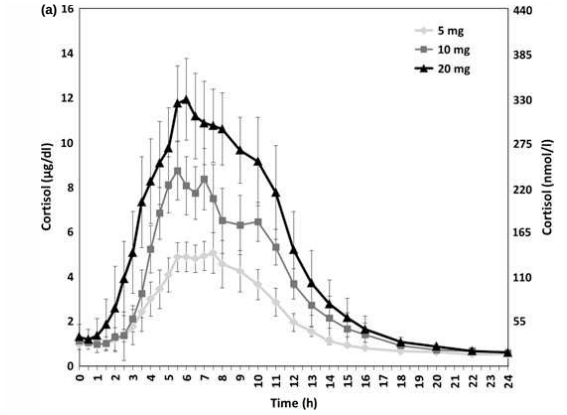
ORIGINAL ARTICLE

An oral multiparticulate, modified-release, hydrocortisone replacement therapy that provides physiological cortisol exposure

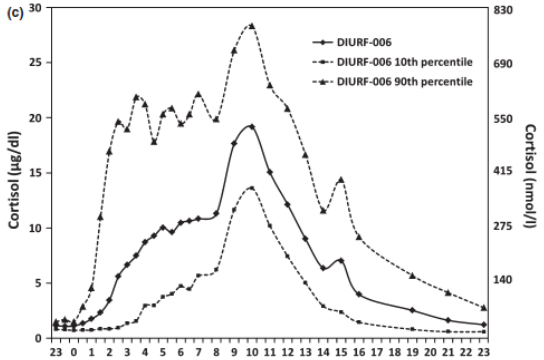
Martin J. Whitaker*,[1], Miguel Debono†,[1], Hiep Huatan*, Deborah P. Merke‡, Wiebke Arlt§ and Richard J. Ross†

Chronocort formulation,DIURF-006,when given as a twice-daily'toothbrush' regimen, 20 mg at night (23:00 h) and 10 mg in the morning (07:00 h) provided cortisol exposure similar to that seen in physiological cortisol levels in a healthy reference population and also to that seen in dexamethasone-suppressed healthy volunteers after a single dose of 30-mg hydrocortisone.

Dose–response of DIURF-006; 5, 10 and 20 mg



Twice-daily dosing at 23:00 and 07:00 h with DIURF-006; 20 and 10 mg in dexamethasone- suppressed healthy male volunteers.



DIURF-006

Migliore esposizione sistemica al cortisolo nelle prime ore notturne

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

J Clin Endocrinol Metab, March 2015, 100(3):1137–1145

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

Continuous subcutaneous hydrocortisone infusion in Addison's disease

Kristian Løvås[1,2] and Eystein S Husebye[1,2]

[1]Division of Endocrinology, Institute of Medicine, University of Bergen, and [2]Department of Medicine, Haukeland University Hospital, 5021 Bergen, Norway

(Correspondence should be addressed to K Løvås; Email: kristian.lovas@med.uib.no)

European Journal of Endocrinology (2007)

Continuous Subcutaneous Hydrocortisone Infusion versus Oral Hydrocortisone Replacement for Treatment of Addison's Disease: A Randomized Clinical Trial

J Clin Endocrinol Metab, May 2014, 99(5):1665–1674

Marianne Øksnes, Sigridur Björnsdottir, Magnus Isaksson, Paal Methlie, Siri Carlsen, Roy M. Nilsen, Jan-Erik Broman, Kai Triebner, Olle Kämpe, Anna-Lena Hulting, Sophie Bensing, Eystein S. Husebye, and Kristian Løvås

Continuous Subcutaneous Hydrocortisone Infusion Therapy in Addison's Disease: A Randomized, Placebo-Controlled Clinical Trial

Lucia Gagliardi, Marni A. Nenke, Tilenka R. J. Thynne, Jenny von der Borch, Wayne A. Rankin, David E. Henley, Jane Sorbello, Warrick J. Inder, and David J. Torpy

J Clin Endocrinol Metab, November 2014, 99(11):4149–4157

- **Microinfusore sottocutaneo: idrocortisone 50mg/ml (durata 3 giorni)**
- **10 mg/m2 per superficie corporea die**
- **Simulazione della normale secrezione circadiana di cortisolo**
- **Replicando il normale ritmo del cortisolo:**

  riduzione di ACTH e miglioramento QoL
- **Costo: pz selezionati in cui non si riesce ad ottenere un compenso con la tradizionale terapia**

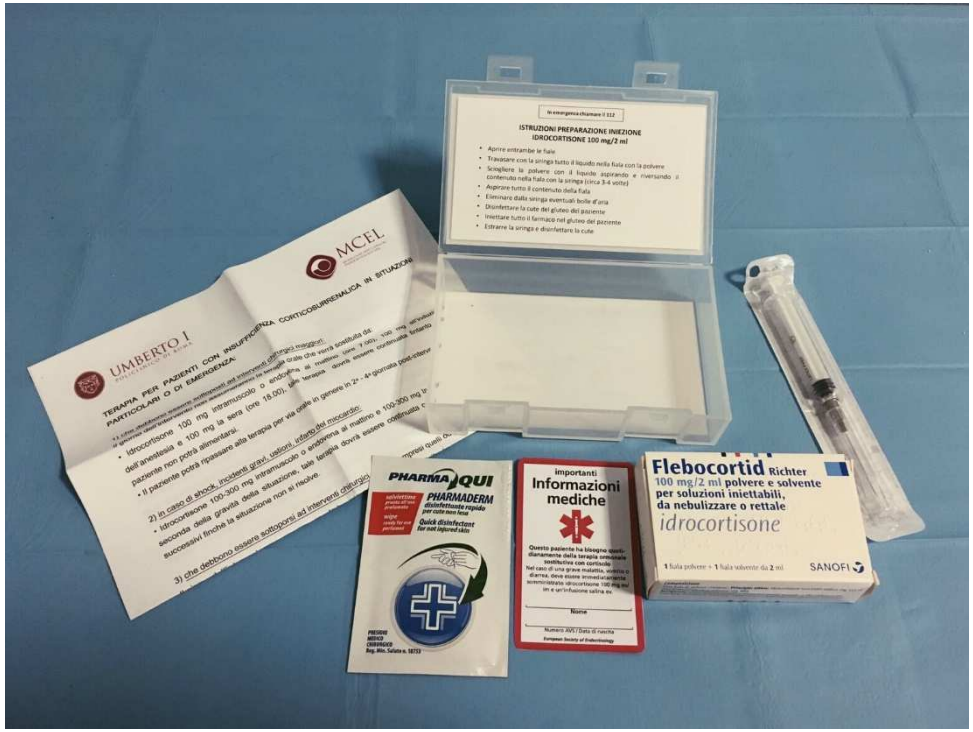
Title: Management of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline

3.5 We recommend monitoring glucocorticoid replacement using clinical assessment including body weight, postural blood pressure, energy levels, signs of frank glucocorticoid excess, and growth velocity in children. There are no valid parameters for biochemical monitoring of glucocorticoid replacement. (Grade 2/⊕⊕⊕O)

Monitoring of glucocorticoid replacement relies primarily on clinical assessment. Symptoms and signs of over-replacement are weight gain, insomnia, and peripheral edema. Insufficient dosing is characterized by nausea, poor appetite, weight loss, lethargy and hyperpigmentation. Detailed questioning about the patient's daily habits, working patterns (e.g. shift work), general feelings of energy, mental concentration, daytime somnolence, dips in energy can help fine-tune when tablets should be taken, how often and at what dose. Compliance and use of extra doses should be mapped. In cases when malabsorption is suspected serum or salivary cortisol day curve monitoring may be useful to guide dosing. Although elevated concentrations of serum ACTH may indicate underreplacement, the assessment of ACTH is not sufficiently validated in the context of glucocorticoid therapy.

KIT DI EMERGENZA

KIT DI EMERGENZA



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