Approcci interdisciplinari in reumatologia - 7ª edizione

MALATTIE REUMATICHE E DISORDINI ENDOCRINO-METABOLICI

Terapia steroidea personalizzata: possibilità e limiti

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Terapia steroidea (glucocorticoidi)

Table 1 Common clinical uses of systemic corticosteroids

Field of medicine	Disorder(s)
Allergy and respirology	• Moderate to severe asthma exacerbations
	• Acute exacerbations of chronic obstructive pulmonary disease
	• Allergic rhinitis
	• Atopic dermatitis
	• Urticaria/angioedema
	• Anaphylaxis
	• Food and drug allergies
	• Nasal polyps
	• Hypersensitivity pneumonitis
	• Sarcoidosis
	• Acute and chronic eosinophilic pneumonia
	• Interstitial lung disease
Dermatology	• Pemphigus vulgaris
	• Acute, severe contact dermatitis
Endocrinology*	• Adrenal insufficiency
	• Congenital adrenal hyperplasia
Gastroenterology	• Ulcerative colitis
	• Crohn's disease
	• Autoimmune hepatitis
Hematology	• Lymphoma/leukemia
	• Hemolytic anemia
	• Idiopathic thrombocytopenic purpura
Rheumatology/ immunology	• Rheumatoid arthritis
	• Systemic lupus erythematosus
	• Polymyalgia rheumatica
	• Polymyositis/dermatomyositis
	• Polyarteritis
	• Vasculitis
Ophthalmology	• Uveitis
	• Keratoconjunctivitis
Other	• Multiple sclerosis
	• Organ transplantation
	• Nephrotic syndrome
	• Chronic active hepatitis
	• Cerebral edema

... ampiamente utilizzata nella pratica clinica (1-2% del mondo occidentale, 3% nelle donne di età superiore agli 80 anni) per controllare l'attività delle **malattie autoimmuni, infiammatorie e allergiche, neoplasie del sistema ematopoietico, e altre patologie ....**

Table 2 Primary effects of glucocorticoids (GCs) [1]

Anti-inflammatory:	Inhibit inflammation by blocking the action of inflammatory mediators (transrepression), or by inducing anti-inflammatory mediators (transactivation)
Immunosuppressive:	Suppress delayed hypersensitivity reactions by directly affecting T-lymphocytes
Anti-proliferative:	Inhibition of DNA synthesis and epidermal cell turnover
Vasoconstrictive:	Inhibit the action of histamine and other vasoconstrictive mediators

Terapia steroidea (glucocorticoidi)

… In campo reumatologico ….

1940 Watson segnala qualche beneficio in malati di artrite reumatoide con l'impiego di **estratti di corteccia surrenalica**…

1948 Hench ipotizza la possibile esistenza di un ormone surrenale ad azione antireumatica (**sostanza X**) carente nell'artrite reumatoide … impiega per la prima volta il **cortisone** (composto E) per la cura di una giovane paziente di 29 anni…

1995 nasce il **prednisone**, il primo dei derivati semisintetici del cortisone con minori effetti mineraloattivi rispetto al cortisone…

Quali glucocorticoidi ?

GC	Equivalent (replacement) doses (mg)	Anti-inflammatory potency (GR)	MR potency	T ½ (h)	Duration of action (h)
Short-acting					
Cortisone acetate	25	0.8	1.5	0.5	8-12
Hydrocortisone	20	1	2	1.5-2	8-12
Intermediate-acting					
Prednisone	5	4	1	1	18-36
Prednisolone	5	4	1	2-3.5	18-36
Methylprednisolone	4	5	0	1.5-3	18-36
Meprednisone	4	5	0	3.5-4	12-36
Triamcinolone	4	5	0	3.5-4	18-36
Paramethasone	2	10	0	3.5-4	12-36
Fluprednisolone	1.5	15	0	3.5-4	12-36
Long-acting					
Betamethasone	0.6	25-50	0	5.5	36-54
Dexamethasone	0.75	26	0	2-3.5	36-54

Cortone (cp 25 mg)

Idrocortisone (cp 10 mg)

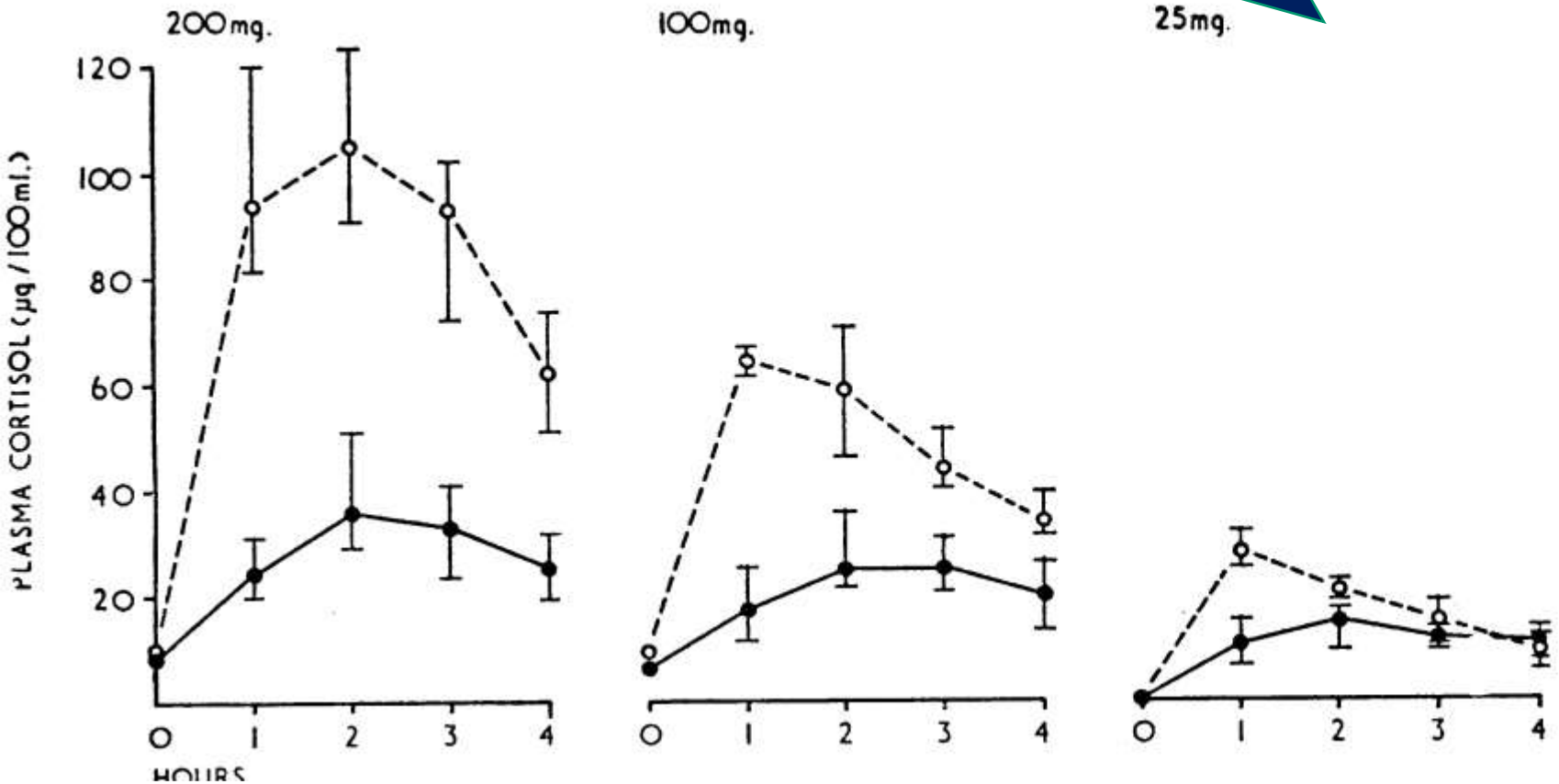


FIG. 1.—Plasma cortisol levels after cortisone indicated by ●——●, and after cortisol indicated by O - - - O. The mean and range of values are for five normal subjects given 200 mg. of each steroid, four normal subjects given 100 mg., and three patients with Addison's disease given 25 mg.

Prednisone- Prednisolone

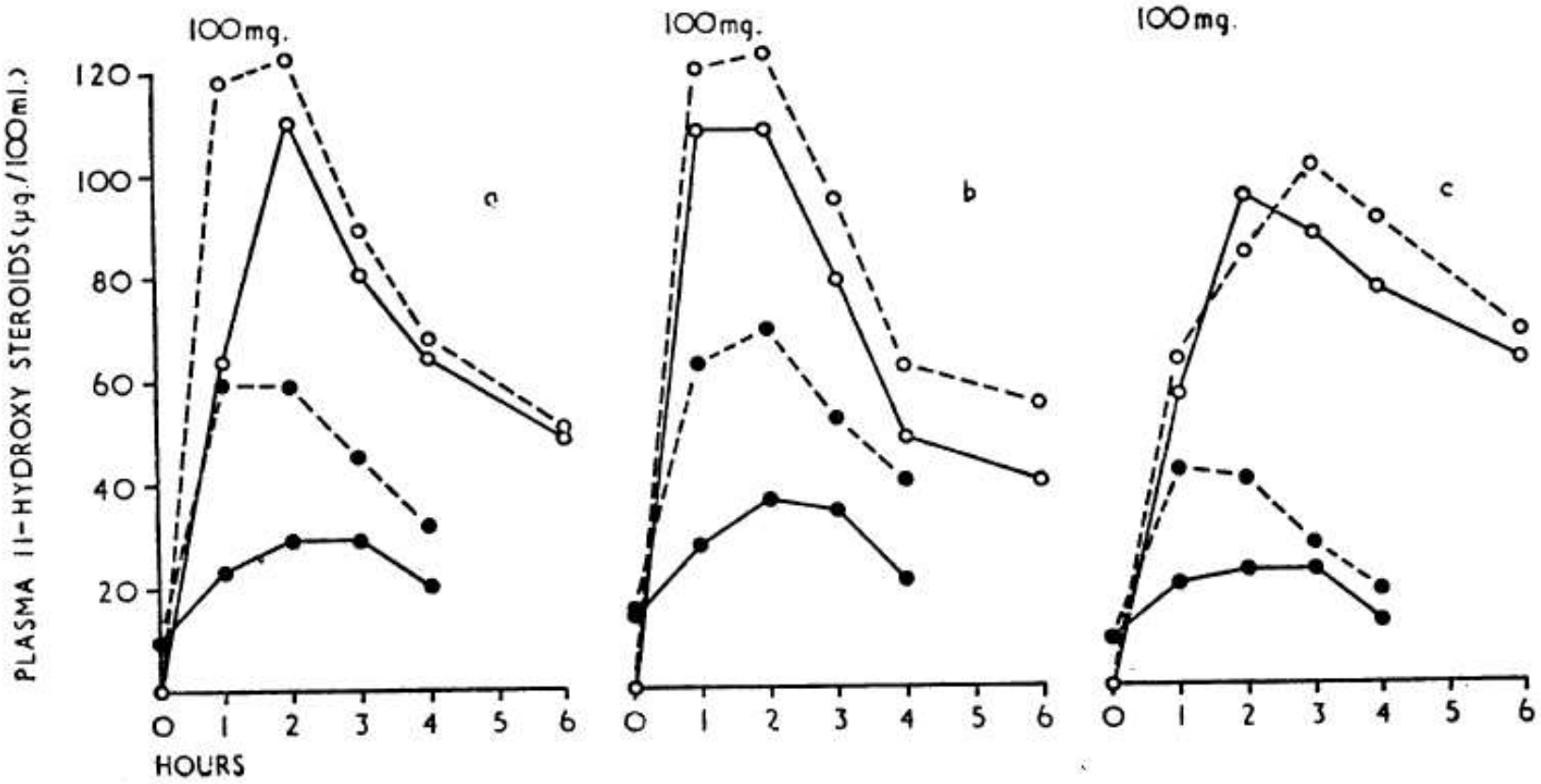
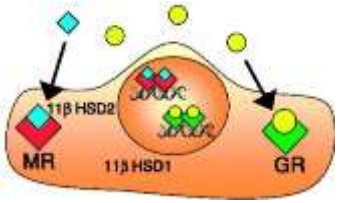
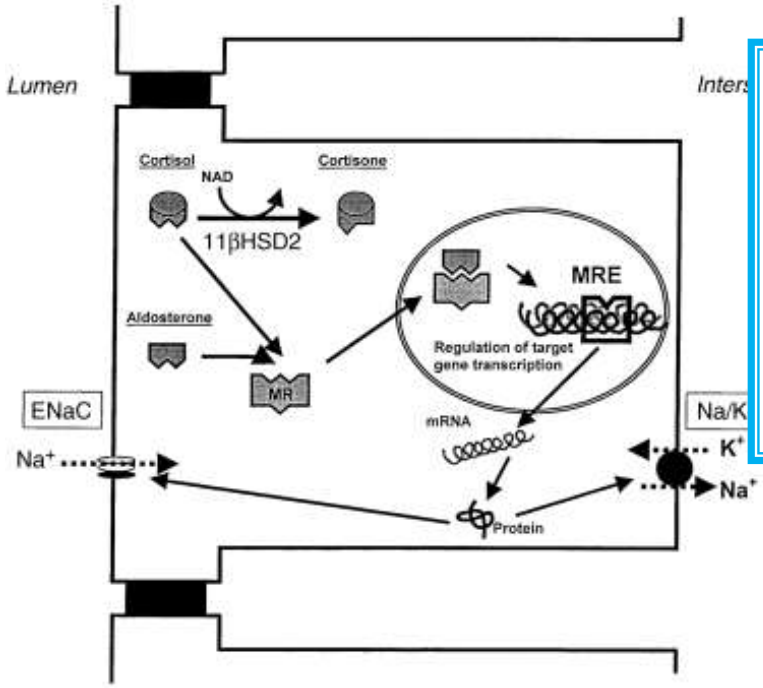


FIG. 2.—Plasma prednisolone levels in three normal subjects, a, b, c, after 100 mg. of prednisone indicated by O——O and after 100 mg. of prednisolone indicated by O - - - O. The lower two curves show plasma cortisol values in the same subjects given 100 mg. cortisone indicated by ●——●, and cortisol indicated by ● - - - ●.

Meccanismo d'azione



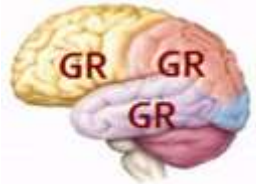


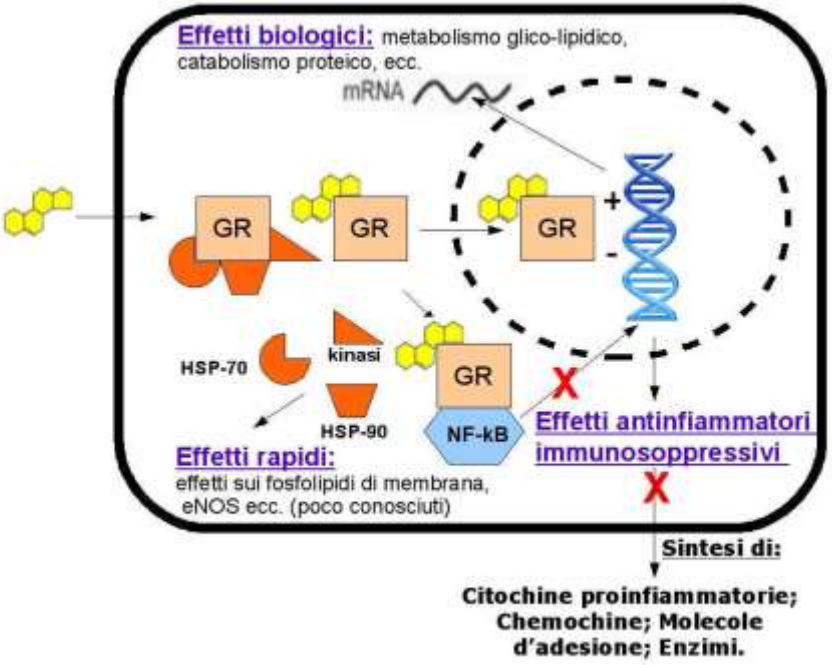
MR
- **alta affinità per GC**
- **non selettivo per aldosterone**
- **espresso solo in alcuni tessuti**

(tubulo renale, gh.sudoripare e salivari, colon, miocardio, endotelio, muscolatura vascolare, ippocampo)

GR
- **bassa affinità per GC**
- **selettivo per GC**
- **espresso in modo ubiquitario**

(SNC, ippocampo, tessuti periferici)



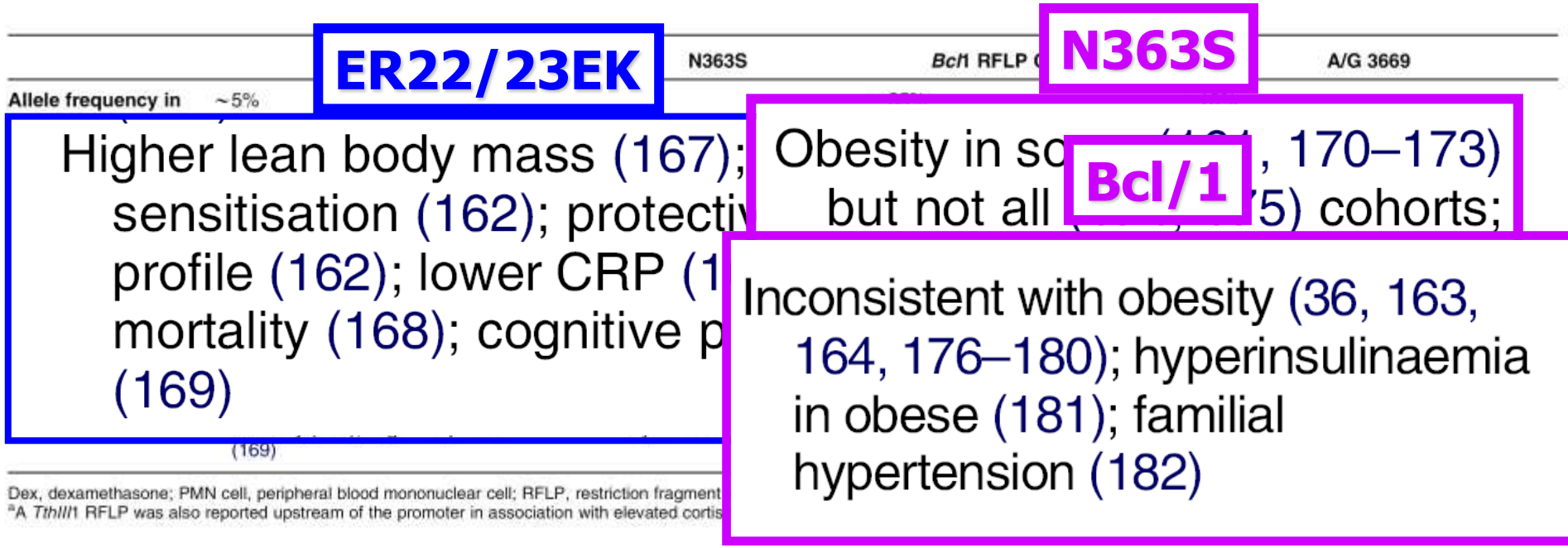


Tre isoforme del GR

- ✓ **GR-α**: modula l'espressione dei GRE
- ✓ **GR-β**: non lega GC/non induce trascrizione genica
- ✓ **GR-γ**: minor attività trascrizionale del GRα

Polimorfismo del GR-α

- ✓ **ER22/23EK**: relativa resistenza ai GC
- ✓ **N363S**: relativa sensibilità ai GC
- ✓ **Bcl/1**: relativa sensibilità ai GC

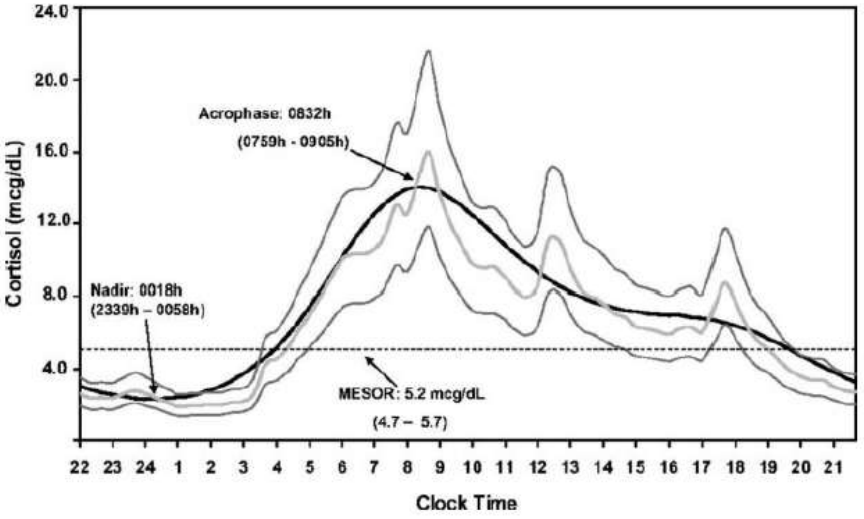


Terapia steroidea personalizzata: possibilità ?

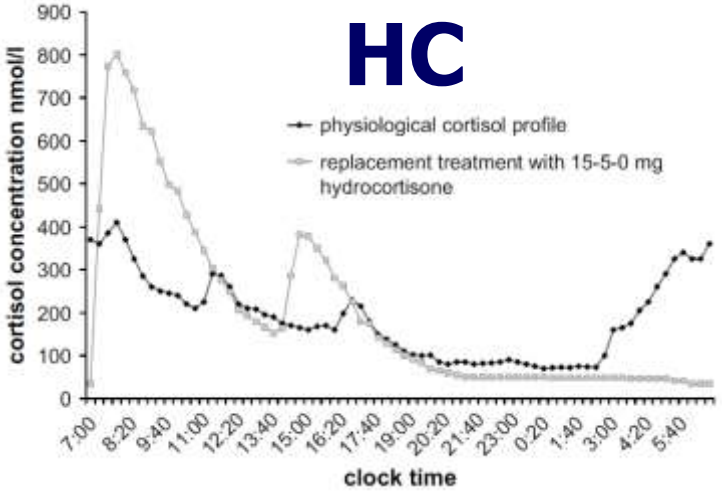
Towards the tailoring of glucocorticoid replacement in adrenal insufficiency: the Italian Society of Endocrinology Expert Opinion

A. M. Isidori[1] · G. Arnaldi[2] · M. Boscaro[3] · A. Falorni[4] · C. Giordano[5] · R. Giordano[6] · R. Pivonello[7] · C. Pozza[1] · E. Sbardella[1] · C. Simeoli[7] · C. Scaroni[3] · A. Lenzi[1] · On behalf of the Italian Society of Endocrinology

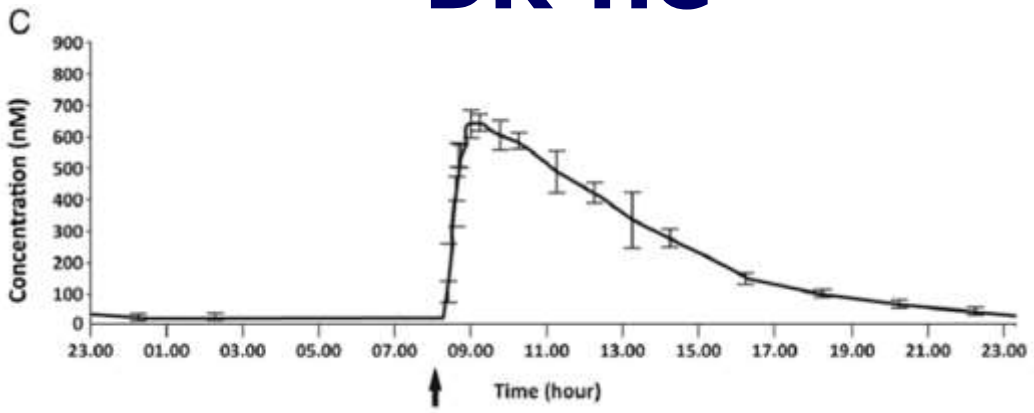
nological Investigation (2020) 43:683–696



HC



DR-HC



Prednisone- Prednisolone

Reduced Final Height Outcome in Congenital Adrenal Hyperplasia under Prednisone Treatment: Deceleration of Growth Velocity during Puberty

Walter Bonfig, Susanne Bechtold, Heinrich Schmidt, Dietrich Knorr, and Hans Peter Schwarz

J Clin Endocrinol Metab, May 2007, 92(5):1635–1639

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**

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

The **EULAR Glucocorticoid Task Force** has already published **several recommendations over the last years** such as those on the standardized nomenclature for GC dosages and treatment regimens, on the management of systemic GC therapy in rheumatic diseases, and on monitoring adverse events of low-dose GC therapy.
Recent work of this group dealt with the question under which conditions long-term treatment with GC has an acceptably **low level of harm**.
As a result, the task force members agreed that the risk of harm is low for the majority of patients at long-term dosages of ≤5 mg prednisone equivalent per day, whereas at dosages of >10 mg/day the risk of harm is elevated. **At dosages between >5 and ≤10 mg/day, patient-specific characteristics determine the risk of harm.** This means **general and glucocorticoid-associated risk factors** and **protective factors** such as a healthy lifestyle should be taken into account when evaluating the actual and future risk.

GC prescribed in conjunction with a maintenance treatment with early RA have proven to be symptomatically and structurally effective, even at low doses of 7.5 mg/d of prednisolone. Nonetheless, in light of the risk of long-term adverse events that increase with the cumulative dose, they should be prescribed for a limited time only.

In light of the risks associated with cumulative doses of glucocorticoids, the most recent EULAR 2016 guidelines [32] recommend limiting the use of GC to when they are necessary, at the lowest dose possible, and for the shortest time possible (< 6 months). Glucocorticoids can also be recommended for a short time to treat flare-ups upon a change in the maintenance therapy with established RA.

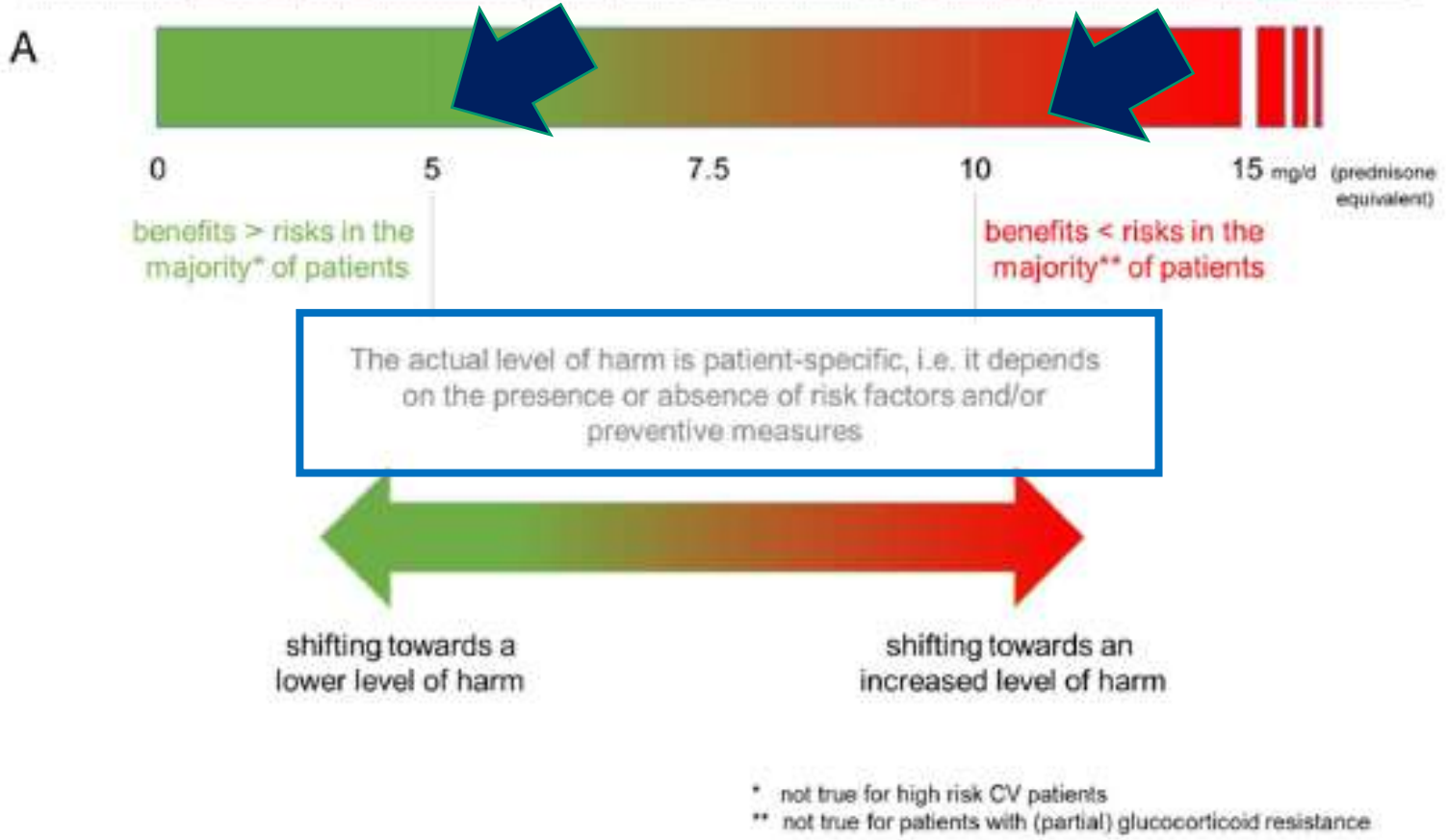
Initiation of long-term oral glucocorticoid therapy with early RA also exposes to a risk of self-medication and a "psychological" dependency, which are two factors that can compromise the chances of withdrawal after several months of treatment. The use of parenteral forms initially (IV or IM forms) as well as iterative injections have been shown to be effective and could be recommended upon initiation of a first maintenance treatment, thereby allowing long-term oral GC to be avoided and to maintain control of the cumulative doses of GC in patients with recent-onset RA.

Joint Bone Spine 85 (2018) 417–422

Defining conditions where long-term glucocorticoid treatment has an acceptably low level of harm to facilitate implementation of existing recommendations: viewpoints from an EULAR task force

Cindy Strehl,[1] Johannes W J Bijlsma,[2,3] Maarten de Wit,[4] Maarten Boers,[3,5] Nele Caeyers,[6] Maurizio Cutolo,[7] Bhaskar Dasgupta,[8] William G Dixon,[9] Rinie Geenen,[10] Tom W J Huizinga,[11] Alison Kent,[12] Annette Ladefoged de Thurah,[13] Joachim Listing,[14] Xavier Mariette,[15,16] David W Ray,[17] Hans U Scherer,[11] Raphaèle Seror,[15,16] Cornelia M Spies,[1] Simon Tarp,[18] Dieter Wiek,[19] Kevin L Winthrop,[20] Frank Buttgereit[1]

Ann Rheum Dis 2016;**75**:952–957. doi:10.1136/annrheumdis-2015-208916



Pazienti considerati a basso rischio

	Factors	References
General	early diagnosis, low disease activity, low cumulative glucocorticoid dosage, healthy life style (especially cessation of smoking, low alcohol consumption), monitoring and treatment of risk factors and co-morbidities	[1] [21] [37]
Glucocorticoid-induced osteoporosis	sufficient vitamin D & calcium intake, exercise, muscle strengthening, prescription on indication: bisphosphonates, osteoanabolic drugs, selective oestrogen receptor modulators	[38] [39] [40] [41] [42]
Infections	screening for infections, vaccination, usage of risk scores before therapy, follow rules of conduct (avoiding infected persons, appropriate wound care, washing hands, good sleep)	[44] [50] [52]
Carbohydrate metabolism	healthy diet, appropriate exercise, weight loss for obese patients, prescription on indication: hydroxychloroquine, diuretics	[58] [59]
Cardiovascular	diet in low saturated fat & calories, physical activity, weight normalization, sodium restriction, follow the EULAR-recommendations for cardiovascular risk management (including medications like statins or angiotensin-converting enzyme inhibitors on indication)	[2] [60] [70] [75] [76] [77]

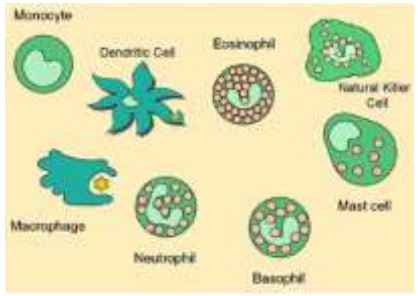
Pazienti considerati ad alto rischio

Patient specific factors shifting towards an increased level of harm

	Factors	References
General	high disease activity, high cumulative glucocorticoid dosage, lifestyle (especially bad nutrition, smoking, high alcohol consumption)	[17] [28] [66]
Glucocorticoid-induced osteoporosis	age > 60 years, female sex, low body weight, low bone mineral density, family history of osteoporosis, prevalent fractures, low calcium intake	[23] [35] [36] [37] [38]
Infections	age > 60, male sex, comorbidities (e.g. chronic lung disease, coronary heart disease, heart failure, peripheral vascular diseases, diabetes mellitus, hepatitis C, chronic renal diseases, leukopenia, neurological disease) high number of treatment failures, prior serious infections	[28] [43] [46] [47] [48] [49] [50] [51]
Carbohydrate metabolism	higher age, high body mass index, genetic predisposition, long disease duration	[54] [55]
Cardiovascular	higher age, male sex, severe extra-articular disease manifestation, RF positivity, ACPA positivity, comorbidities (e.g. hypertension, diabetes, dyslipidaemia, obesity, Cushing's syndrome)	[29] [47] [65] [67] [72] [73] [74]

Glucocorticoidi: effetti biologici = limiti ?

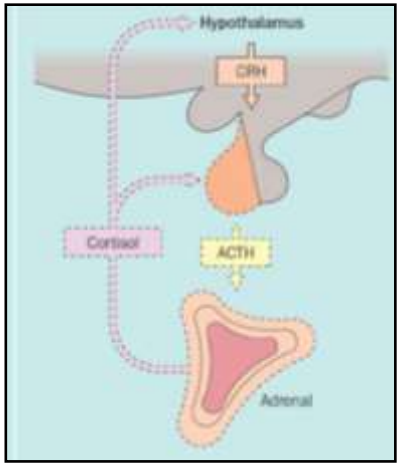
Sistema immunitario



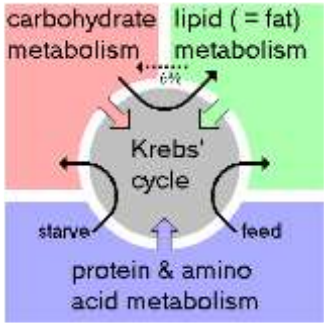
SNC

Muscolo

HPA



Metabolismo



GC

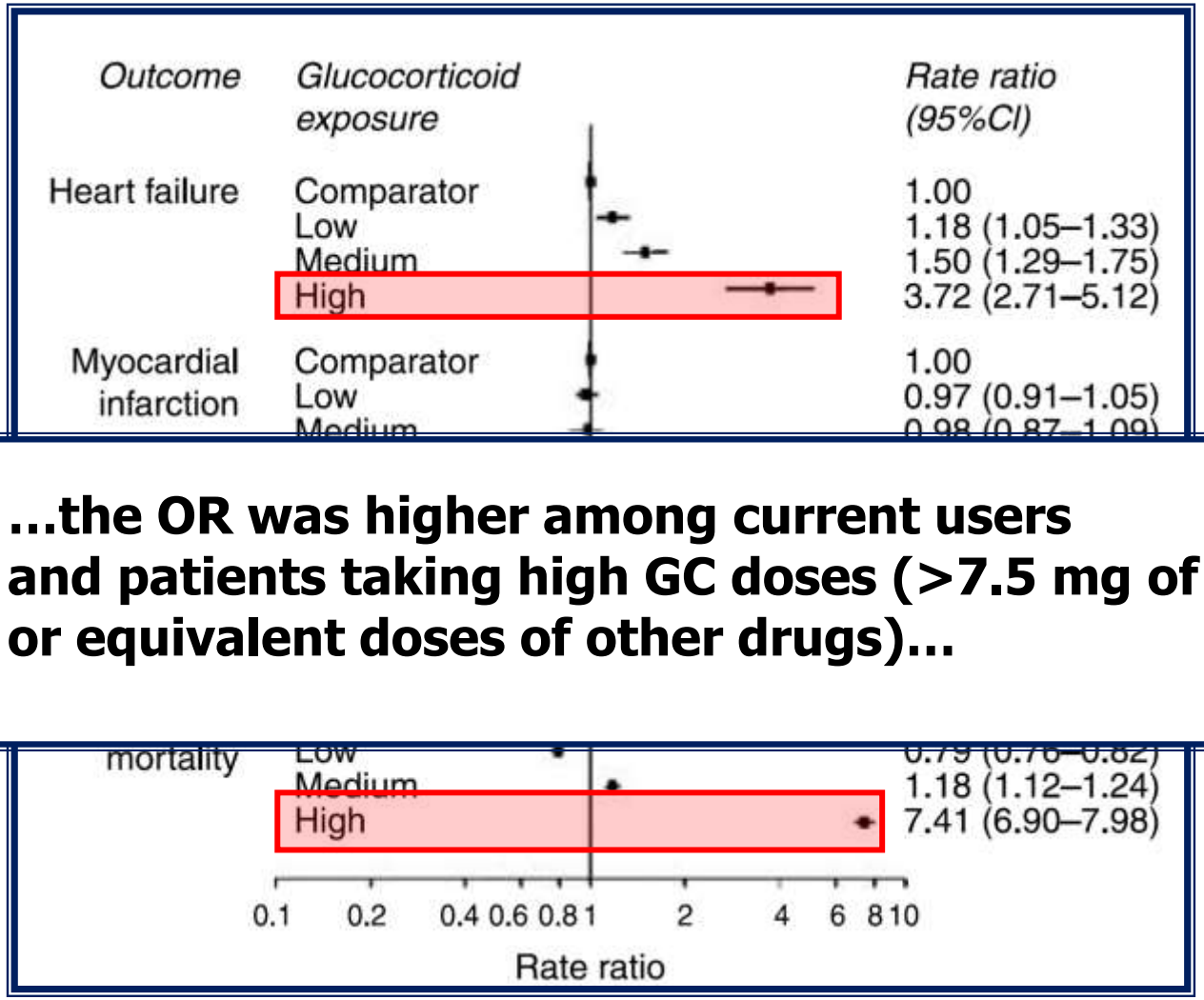
Composizione corporea

Osso

Sistema CV

Taking glucocorticoids by prescriptions is associated with subsequent cardiovascular disease

Wei L, Mac Donald M and Walker BR *Ann Int Med 2004;141:764-70*



…the OR was higher among current users and patients taking high GC doses (>7.5 mg of prednisolone per day or equivalent doses of other drugs)…

Effects of synthetic glucocorticoids

Adrenal gland

Adrenal atrophy, Cushing's syndrome appearance (moon face, hirsutism and buffalo hump, weight gain, and lipid redistribution)

Central nervous system

Changes in behavior, cognition, memory, and mood (i.e., glucocorticoid-induced psychoses), cerebral atrophy, suppression of the hypothalamus-pituitary-adrenal

Concomitant signs and symptoms of:

CUSHING'S SYNDROME

Cardiovascular system & metabolism
Dyslipidemia, hypertension, thrombosis, vasculitis, hyperglycemia

Kidney
Increased sodium retention and potassium excretion

Musculoskeletal system
Bone necrosis, muscle atrophy, osteoporosis, retardation of longitudinal bone growth

Immune system
Broad immunosuppression, activation of latent viruses, candidiasis

Skin
Atrophy, delayed wound healing, erythema, hypertrichosis, dermatitis, petechiae, acne, striae rubrae, telangiectasia, bruising

Gastrointestinal tract
Gastrointestinal bleeding, pancreatitis, peptic ulcer

Reproductive system
Delayed puberty, fetal growth retardation, hypogonadism

CENTRAL ADRENAL INSUFFICIENCY

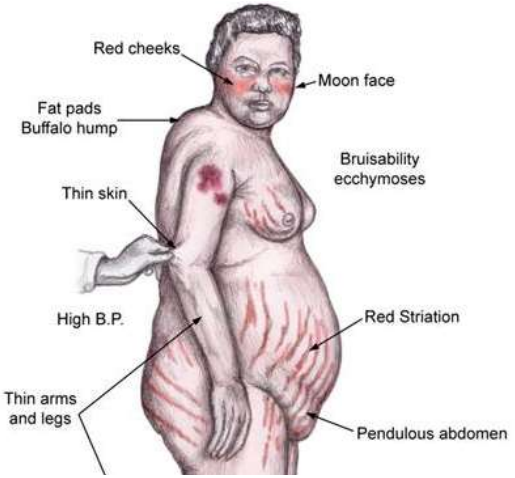
Risk of adrenal crisis

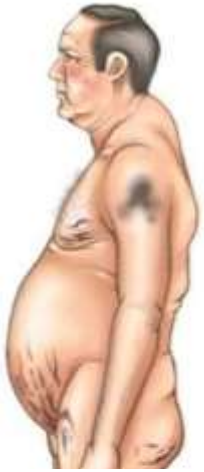
Paragliola RM et al., *Int J Mol Sci 2017; 18: 2201*

Exogenous Cushing's syndrome

Rachel L. Hopkins, MD, Matthew C. Leinung, MD*

Endocrinol Metab Clin N Am
34 (2005) 371–384





… **All available forms of steroids with glucocorticoids activity** are capable of producing Cushing's syndrome…

… The development of Cushingoid signs and symptoms is generally **related to dose and duration of treatment.**
Although **supra-physiological doses** are usually required before patients manifest significant **Cushingoid effects**, **some patients**, in particular those on GCs following renal transplant, can develop Cushingoid appearance with chronic administration of **lower doses as little as 5 mg/d of prednisone**…

Dose Dependency of Iatrogenic Glucocorticoid Excess and Adrenal Insufficiency and Mortality: A Cohort Study in England

Teumzghi F. Mebrahtu,[1] Ann W. Morgan,[2,3] Adam Keeley,[4] Paul D. Baxter,[2] Paul M. Stewart,[3,5] and Mar Pujades-Rodriguez[6]

J Clin Endocrinol Metab, September 2019, 104(9):3757–3767

Retrospective, record-linkage, open-cohort study spanning primary and hospital care in England
70,683 **oral glucocorticoid users** (49,6% polymyalgia rheumatica, 28.3% rheumatoid arthitis) aged ≥ 18 years, registered in 389 practices in 1998 to 2017

Table 4. Observation Time, Overall Incidence Rates, and Time-Variant Oral Glucocorticoid Prednisolone-Equivalent Dose–Related Incidence Rates of Outcomes

	Adrenal Insufficiency	Cushing Syndrome	Mortality
Total person-y of follow-up	450,816	449,936	451,146
Total incident cases, n (%)	183 (0.3)	248 (0.4)	22, 317 (31.6)
Time at risk per subject, median (IQR), y	5.53 (7.06)	5.52 (7.07)	5.54 (7.07)
Incidence rates per 1000 person-y (95% CI)			
Overall	0.41 (0.35–0.47)	0.55 (0.49–0.62)	49.47 (48.82–50.12)
Daily oral dose			
Nonuse period	0.30 (0.25–0.37)	0.28 (0.23–0.35)	47.27 (46.55–48.01)
>0 to 4.9 mg	0.60 (0.39–0.94)	0.33 (0.18–0.60)	36.09 (34.10—38.20)
5.0–7.4 mg	0.58 (0.35–0.99)	0.63 (0.38–1.04)	61.57 (58.50–64.79)
≥7.5 mg	0.86 (0.65–1.15)	2.37 (1.99–2.83)	66.38 (64.23–68.61)
Overall cumulative dose			
>0 to 959.9 mg	0.08 (0.05–0.16)	0.21 (0.14–0.31)	30.43 (29.46–31.43)
960–3054.9 mg	0.21 (0.14–0.30)	0.64 (0.52–0.80)	42.61 (41.48–43.76)
≥3055 mg	0.71 (0.61–0.84)	0.69 (0.58–0.81)	64.68 (63.59–65.78)
Cumulative dose in past y			
>0 to 959.9 mg	1.91 (1.37–2.66)	1.86 (1.33–2.60)	272.45 (265.00–280.11)
960–3054.9 mg	9.50 (7.88–11.47)	11.77 (9.94–13.93)	743.19 (727.56–759.17)
≥3055 mg	30.48 (22.27–41.71)	60.90 (48.78–76.03)	1,817.94 (1744.80–1894.15)

Dose Dependency of Iatrogenic Glucocorticoid Excess and Adrenal Insufficiency and Mortality: A Cohort Study in England

Teumzghi F. Mebrahtu,[1] Ann W. Morgan,[2,3] Adam Keeley,[4] Paul D. Baxter,[2] Paul M. Stewart,[3,5] and Mar Pujades-Rodriguez[6]

J Clin Endocrinol Metab, September 2019, 104(9):3757–3767

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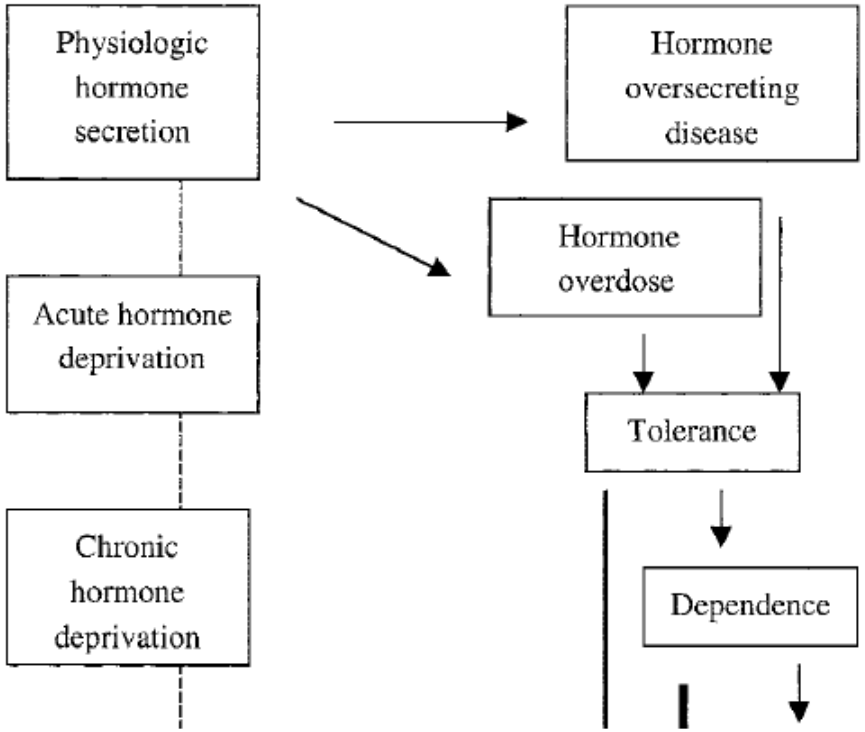
for every increase in daily dose of 5 mg the risk increased by 9%

Table 5. Time-Variant Prescribed Prednisolone-Equivalent Dose of Oral Glucocorticoids and the Risks of Adrenal Insufficiency, Cushing Syndrome, and Death

	Hazard Ratios With 95% CI		
	Adrenal Insufficiency[a]	Cushing Syndrome[a]	Mortality[b]
Current dose per 5 mg/d	1.07 (1.04–1.09)	1.09 (1.08–1.11)	1.06 (1.05–1.06)
Current dose category (ref: nonuse period)			
>0 to 4.9 mg	2.10 (1.29–3.40)	1.20 (0.64–2.25)	0.63 (0.59–0.67)
5.0–7.4 mg	1.94 (1.11–3.41)	2.07 (1.20–3.57)	1.03 (0.98–1.09)
≥7.5mg	2.95 (2.07–4.21)	6.64 (5.03–8.78)	1.20 (1.16–1.25)
Overall cumulative dose (per 1000 mg)	1.09 (1.08–1.10)	1.10 (1.08–1.11)	1.03 (1.03–1.04)
Overall cumulative dose category (ref: >0 to 959.9 mg)			
960–3054.9 mg	2.75 (1.32–5.74)	4.24 (2.68–6.69)	1.19 (1.14–1.24)
≥3055 mg	14.16 (7.25–27.64)	11.00 (6.95–17.43)	1.64 (1.57–1.71)
Cumulative dose for the past y (per 1000 mg)	2.25 (2.15–2.35)	2.31 (2.23–2.40)	2.05 (2.04–2.06)
Cumulative dose category for the past y (ref: >0 to 959.9 mg)			
960–3054.9 mg	4.98 (3.40–7.30)	6.83 (4.67–9.99)	2.65 (2.56–2.75)
≥3055 mg	15.38 (9.72–24.35)	37.03 (24.58–55.78)	6.66 (6.34–7.00)



Do glucocorticoids induce addiction in humans?

R. Giordano[1,2] · F. Guaraldi[2] · M. Mazzoli[2] · E. Ghigo[2]

J Endocrinol Invest (2017) 40:881–883

Adrenal insufficiency

Withdrawal syndrome

Hochberg Z et al., *Endocr Rev 2003; 24: 523-538*

Adrenal Insufficiency in Corticosteroids Use: Systematic Review and Meta-Analysis

Leonie H. A. Broersen, Alberto M. Pereira, Jens Otto L. Jørgensen, and Olaf M. Dekkers

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J Clin Endocrinol Metab, June 2015, 100(6):2171–2180

1975-February 2014
74 articles
136 study groups (3753 participants)

Systemic glucocorticoid therapy and adrenal insufficiency in adults: A systematic review

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1946-2016
73 articles (3166 patients)

Seminars in Arthritis and Rheumatism 46 (2016) 133–141

administration form

Administration	Studies	Patients	Absolute risk (95% CI
Oral	38	1419	48.7 (36.9, 60.6)
Inhalation	60	1418	7.8 (4.2, 13.9)
Topical	15	320	4.7 (1.1, 18.5)
Nasal	8	173	4.2 (0.5, 28.9)
Intra–articular	4	69	52.2 (40.5, 63.6)
Multiple forms	11	354	42.7 (28.6, 58.0)

Glucocorticoid Route
Oral
IM
IV
Multiple

duration - dose

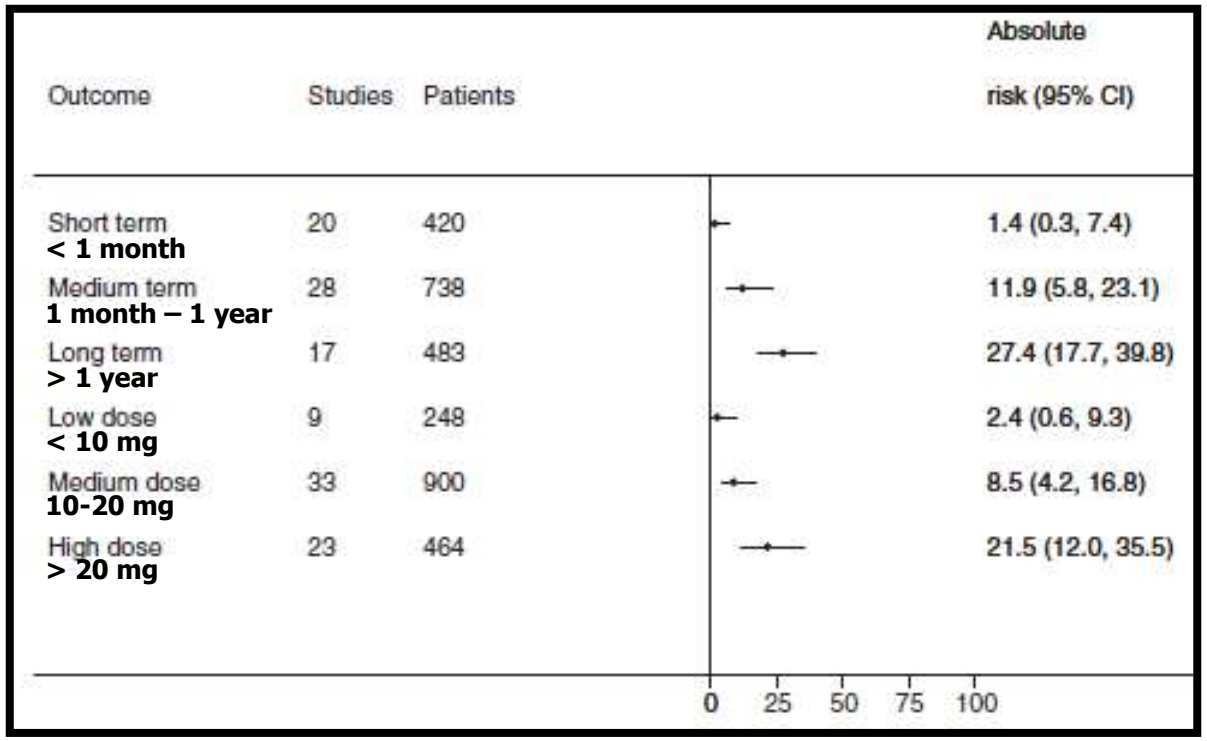
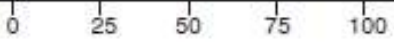


Table 3
Percentage of patients per group with AI by glucocorticoid dose, duration or cumulative dose.

	Total number of patients	Number of groups	Median (range) group size	Median (IQR), % AI	Range, % AI
Average daily dose*					
<5 mg/day	371	15	21 (6–63)	22.7 (11–36)	0–62
5–10 mg/day	703	22	22 (7–86)	43.7 (38–58)	14–80
10–20 mg/day	623	16	19 (3–279)	33.3 (22–80)	0–100
20+ mg/day	527	26	8 (2–100)	16.3 (0–71)	0–100
Duration					
<4weeks	378	15	9 (4–86)	36.4% (0–89%)	0–100%
4–52 weeks	1533	36	20 (5–399)	33.9% (12–55%)	0–92%
52+ weeks	1093	37	19 (3–150)	42% (26–65%)	0–100%
Cumulative dose*					
<0.5g	702	28	19 (2–86)	35.4% (11–54%)	0–100%
0.5–5g	804	23	10 (4–279)	14% (0–40%)	0–89%
5+ g	491	13	23 (3–150)	50% (35–66%)	0–100%

disease

Condition	Studies	Patients	Absolute risk (95% CI)
Asthma	68	1692	11.1 (6.8, 17.7)
Asthma – inhalation only	54	1317	6.8 (3.8, 12.0)
Asthma – other administration forms	14	375	43.7 (27.3, 61.6)
Rhinitis/rhinosinusitis	8	195	19.0 (4.8, 52.2)
Psoriasis/atopic dermatitis/lichen planus	12	273	8.9 (2.4, 27.9)
Rheumatic disorders	8	236	39.4 (27.5, 52.6)
Renal transplant	8	176	56.2 (42.9, 68.6)
Haematological cancers	4	20	60.0 (38.0, 78.6)
Nasal polyposis	2	52	46.2 (33.2, 59.7)
Cystic fibrosis	3	49	49.0 (35.4, 62.7)
Crohn's disease	2	69	52.2 (40.5, 63.6)



Glucocorticoid indication
Musculoskeletal
Respiratory
Neoplasms
Digestive system
Nervous system
Transplant
Multiple

Dose Dependency of Iatrogenic Glucocorticoid Excess and Adrenal Insufficiency and Mortality: A Cohort Study in England

Teumzghi F. Mebrahtu,[1] Ann W. Morgan,[2,3] Adam Keeley,[4] Paul D. Baxter,[2] Paul M. Stewart,[3,5] and Mar Pujades-Rodriguez[6]

J Clin Endocrinol Metab, September 2019, 104(9):3757–3767

Retrospective, record-linkage, open-cohort study spanning primary and hospital care in England
70,683 **oral glucocorticoid users** (49,6% polymyalgia rheumatica, 28.3% rheumatoid arthitis) aged ≥ 18 years, registered in 389 practices in 1998 to 2017

Table 4. Observation Time, Overall Incidence Rates, and Time-Variant Oral Glucocorticoid Prednisolone-Equivalent Dose–Related Incidence Rates of Outcomes

	Adrenal Insufficiency	Cushing Syndrome	Mortality
Total person-y of follow-up	450,816	449,936	451,146
Total incident cases, n (%)	183 (0.3)	248 (0.4)	22, 317 (31.6)
Time at risk per subject, median (IQR), y	5.53 (7.06)	5.52 (7.07)	5.54 (7.07)
Incidence rates per 1000 person-y (95% CI)			
Overall	0.41 (0.35–0.47)	0.55 (0.49–0.62)	49.47 (48.82–50.12)
Daily oral dose			
Nonuse period	0.30 (0.25–0.37)	0.28 (0.23–0.35)	47.27 (46.55–48.01)
>0 to 4.9 mg	0.60 (0.39–0.94)	0.33 (0.18–0.60)	36.09 (34.10—38.20)
5.0–7.4 mg	0.58 (0.35–0.99)	0.63 (0.38–1.04)	61.57 (58.50–64.79)
≥7.5 mg	0.86 (0.65–1.15)	2.37 (1.99–2.83)	66.38 (64.23–68.61)
Overall cumulative dose			
>0 to 959.9 mg	0.08 (0.05–0.16)	0.21 (0.14–0.31)	30.43 (29.46–31.43)
960–3054.9 mg	0.21 (0.14–0.30)	0.64 (0.52–0.80)	42.61 (41.48–43.76)
≥3055 mg	0.71 (0.61–0.84)	0.69 (0.58–0.81)	64.68 (63.59–65.78)
Cumulative dose in past y			
>0 to 959.9 mg	1.91 (1.37–2.66)	1.86 (1.33–2.60)	272.45 (265.00–280.11)
960–3054.9 mg	9.50 (7.88–11.47)	11.77 (9.94–13.93)	743.19 (727.56–759.17)
≥3055 mg	30.48 (22.27–41.71)	60.90 (48.78–76.03)	1,817.94 (1744.80–1894.15)

Dose Dependency of Iatrogenic Glucocorticoid Excess and Adrenal Insufficiency and Mortality: A Cohort Study in England

Teumzghi F. Mebrahtu,[1] Ann W. Morgan,[2,3] Adam Keeley,[4] Paul D. Baxter,[2] Paul M. Stewart,[3,5] and Mar Pujades-Rodriguez[6]

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70,683 **oral glucocorticoid users** (49,6% polymyalgia rheumatica, 28.3% rheumatoid arthitis) aged ≥ 18 years, registered in 389 practices in 1998 to 2017

for every increase in daily dose of 5 mg the risk increased by 7%

Table 5. Time-Variant Prescribed Prednisolone-Equivalent Dose of Oral Glucocorticoids and the Risks of Adrenal Insufficiency, Cushing Syndrome, and Death

	Hazard Ratios With 95% CI		
	Adrenal Insufficiency[a]	Cushing Syndrome[a]	Mortality[b]
Current dose per 5 mg/d	1.07 (1.04–1.09)	1.09 (1.08–1.11)	1.06 (1.05–1.06)
Current dose category (ref: nonuse period)			
>0 to 4.9 mg	2.10 (1.29–3.40)	1.20 (0.64–2.25)	0.63 (0.59–0.67)
5.0–7.4 mg	1.94 (1.11–3.41)	2.07 (1.20–3.57)	1.03 (0.98–1.09)
≥7.5mg	2.95 (2.07–4.21)	6.64 (5.03–8.78)	1.20 (1.16–1.25)
Overall cumulative dose (per 1000 mg)	1.09 (1.08–1.10)	1.10 (1.08–1.11)	1.03 (1.03–1.04)
Overall cumulative dose category (ref: >0 to 959.9 mg)			
960–3054.9 mg	2.75 (1.32–5.74)	4.24 (2.68–6.69)	1.19 (1.14–1.24)
≥3055 mg	14.16 (7.25–27.64)	11.00 (6.95–17.43)	1.64 (1.57–1.71)
Cumulative dose for the past y (per 1000 mg)	2.25 (2.15–2.35)	2.31 (2.23–2.40)	2.05 (2.04–2.06)
Cumulative dose category for the past y (ref: >0 to 959.9 mg)			
960–3054.9 mg	4.98 (3.40–7.30)	6.83 (4.67–9.99)	2.65 (2.56–2.75)
≥3055 mg	15.38 (9.72–24.35)	37.03 (24.58–55.78)	6.66 (6.34–7.00)

GC withdrawal syndrome

HPA-axis recovery

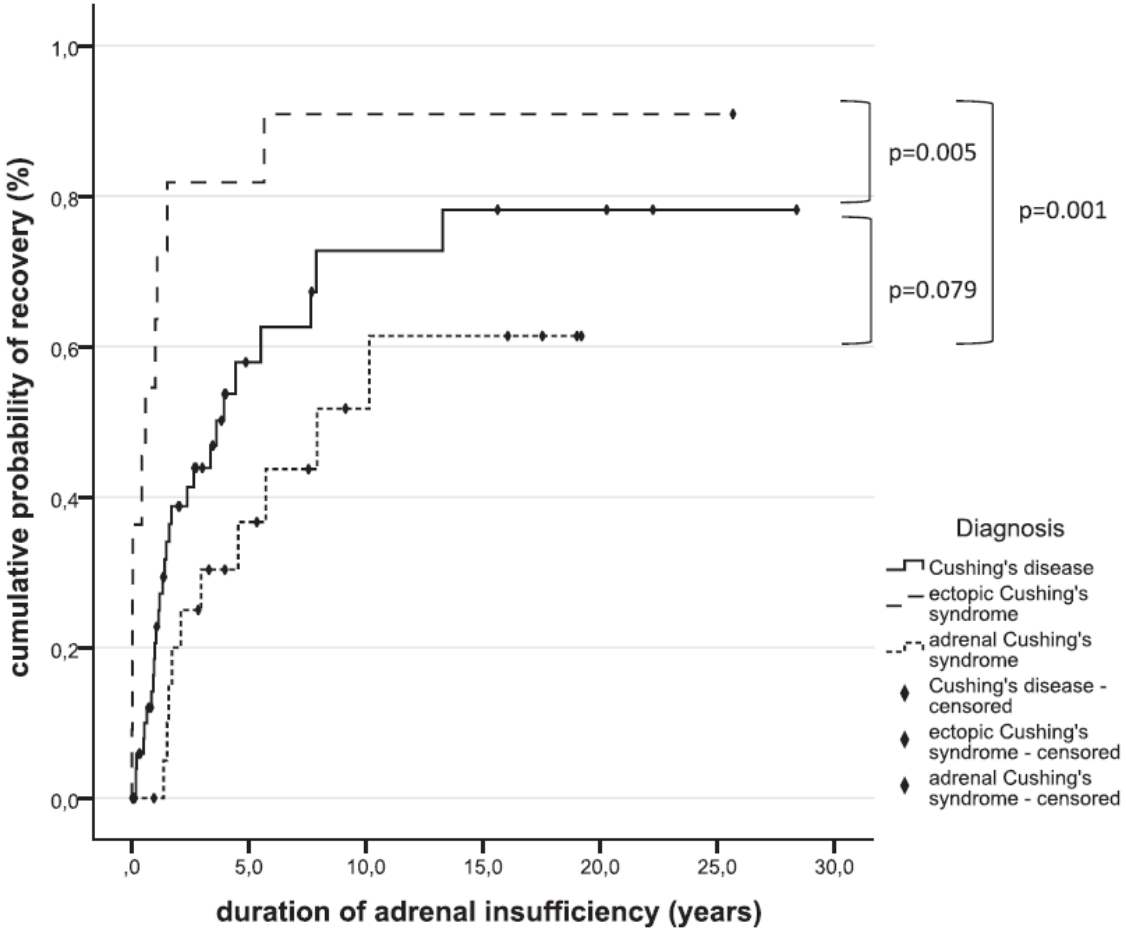
		Mechanisms
1	Relapse of primary illness	
	Suppressed HPA axis	⇓ CRH
	Addisonian crisis	⇓ Glucocorticoid
	Hypercalcemia, hyperphosphatemia	⇑ Vasopressin
2	Nonspecific withdrawal syndrome	⇓ Central noradrenergic system
	Anorexia, nausea, emesis, weight loss	⇓ Central dopaminergic system
	Myalgias, arthralgias, fever, headache	⇓ POMC-related peptides
	Somnolence, lethargy	⇑ Cytokines
	Skin desquamation	⇑ Prostaglandins

Hochberg Z et al., *Endocr Rev 2003; 24: 523-538*

Time to Recovery of Adrenal Function After Curative Surgery for Cushing's Syndrome Depends on Etiology

Christina M. Berr, Guido Di Dalmazi, Andrea Osswald, Katrin Ritzel, Martin Bidlingmaier, Lucas L. Geyer, Marcus Treitl, Klaus Hallfeldt, Walter Rachinger, Nicole Reisch, Rainer Blaser, Jochen Schopohl, Felix Beuschlein, and Martin Reincke

(*J Clin Endocrinol Metab* 100: 1300–1308, 2015)



1983-2014
Retrospective study
91 pts

Recovery at 5 years
Ectopic 82%, 0,6 years
CD 58%, 1,4 years
CS 38%, 2,5 years

Insuffi enalica

GC with drome

Riduzione graduale dei GC

Trattare le condizioni di «stress»

Schemi di riduzione dei GC

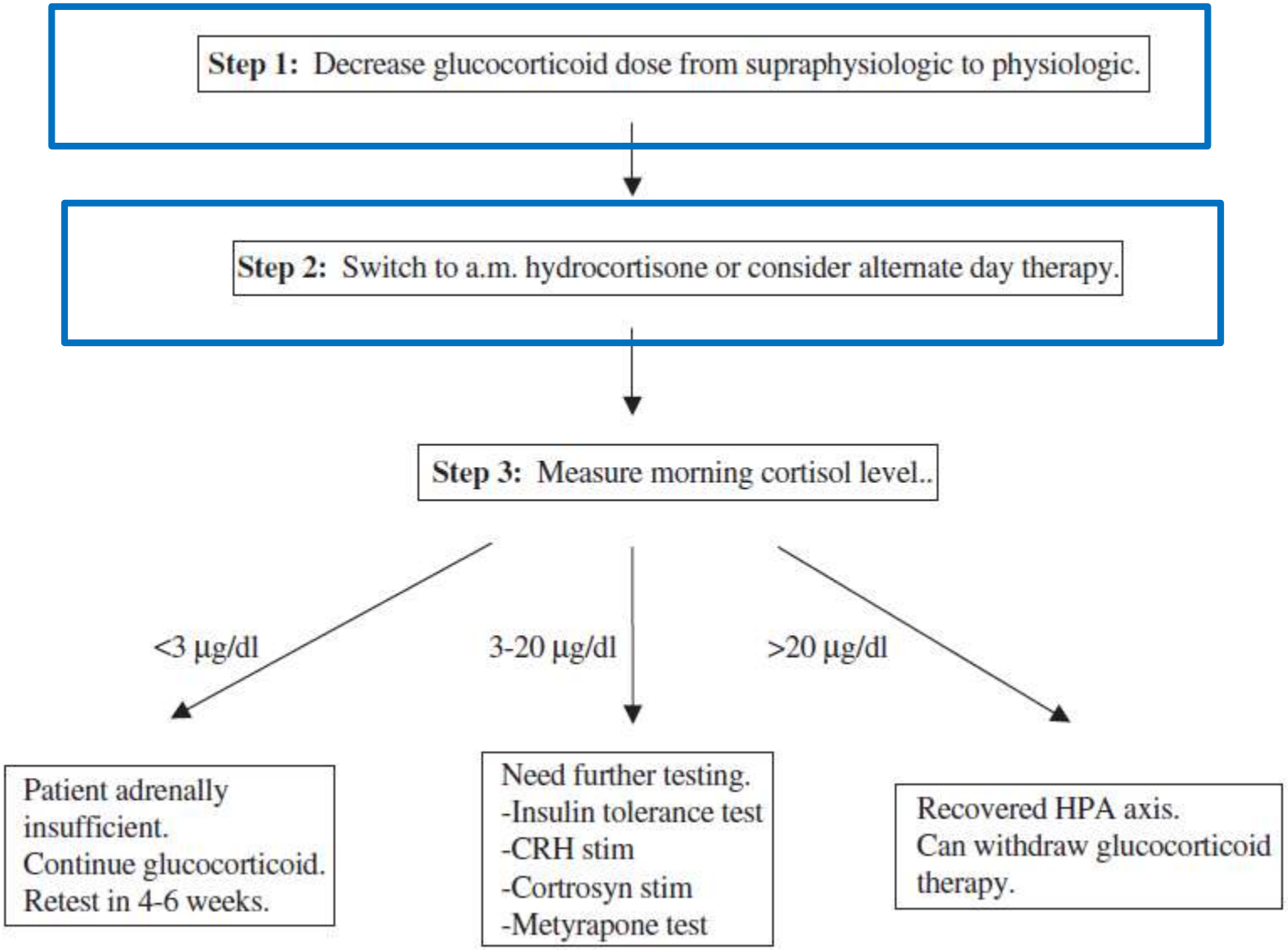
GCs should be tapered as rapidly as clinically feasible… ideally within 3 to 6 months …

EULAR 2016-2017-2018

Table 3 Recommended tapering schedules

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

Guerrero Perez F et al., *JEI 2017; 40: 1175-1181*



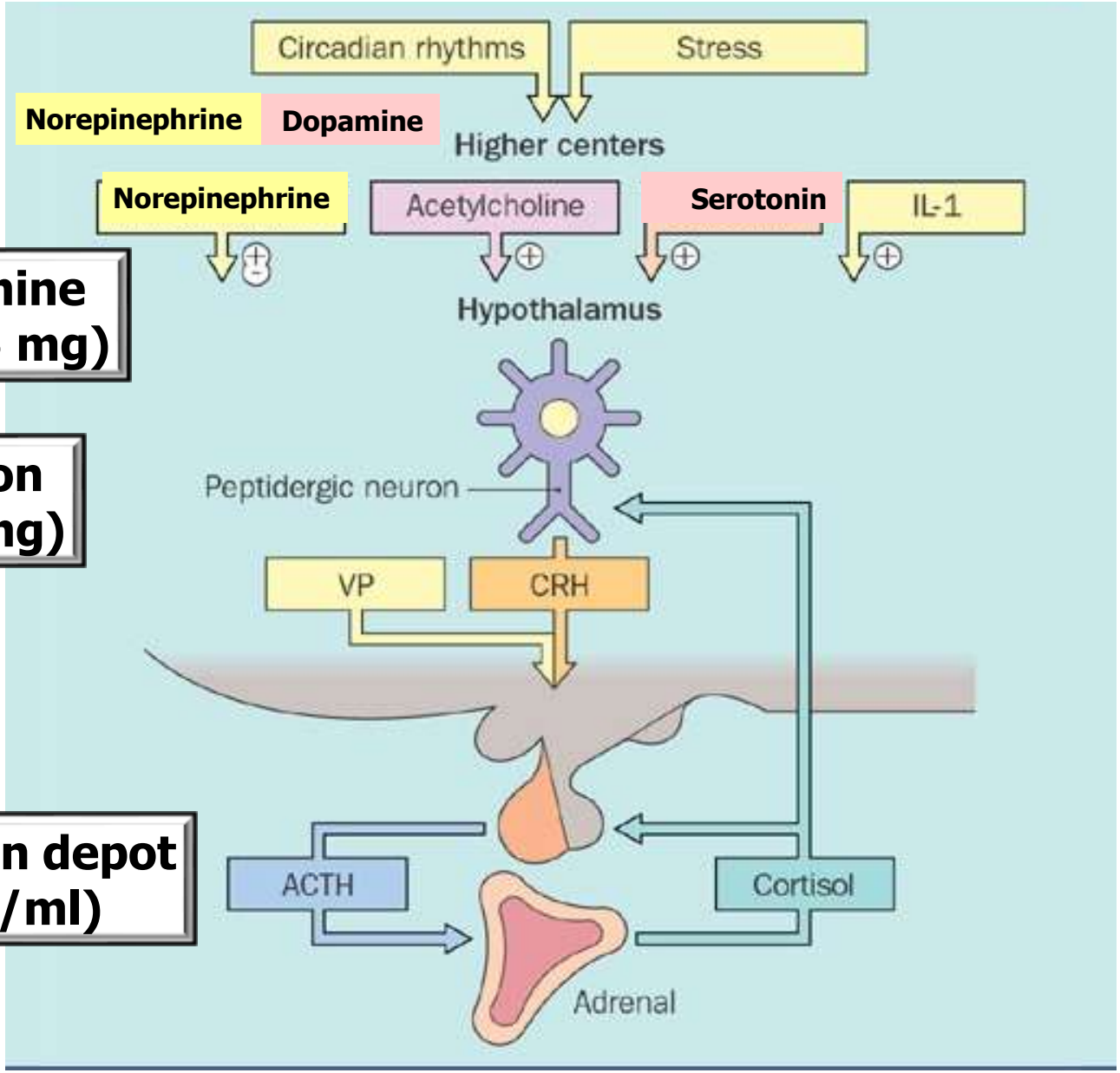
Hopkins RL et al., *Endocrinol Metab Clin N Am 2005; 34: 371-384*

Riattivatori asse HPA ?

Sibutramine (cp 10-15 mg)

Bupropion (cp 150 mg)

Synacthen depot (1 mg/ml)



Trattare lo stress

Table 3. The multi-dimensional nature of the so-called "stress response"

Stressors and Stress Responses: Diversity and Multiplicity	
Main target of exposure to stressor	Physical function, cognitive function, emotional regulation, social integration, development, maturation
Duration of exposure to stressor	Acute, single, repeated, prolonged, chronic
Severity of stressor	Mild, moderate, severe, life threatening
Timing of exposure to stressor	Predictable, unpredictable, dependent on biological time of day, early life, adult life, late life
Type of Response	Homeostatic (adaptive, return to baseline set point) Allostatic (maladaptive, variable set point)

Onster R et al., *Endocr Rev 2016;*

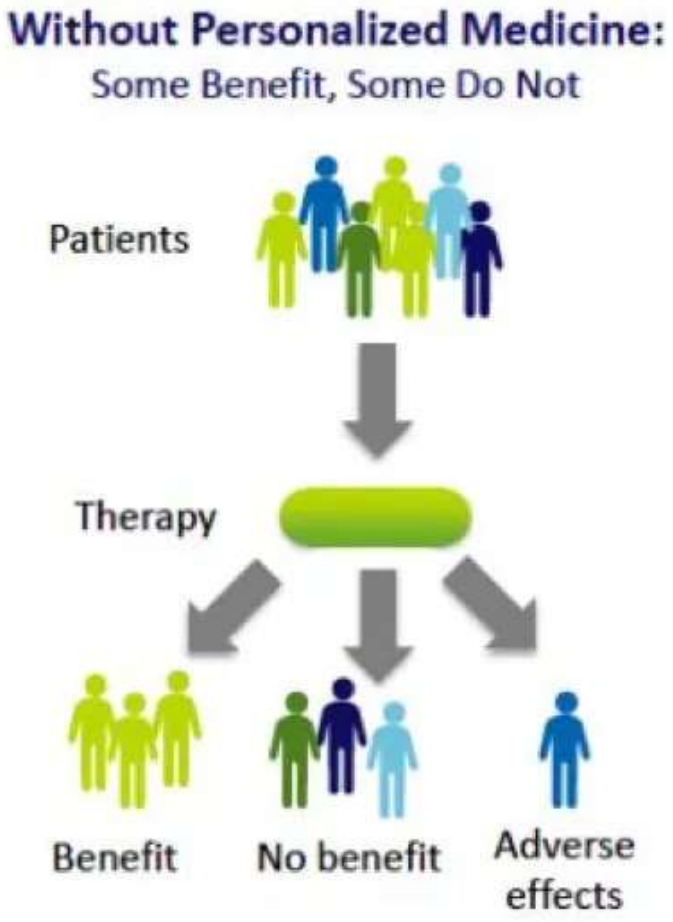
Procedure/Illness	*Cortisol Levels*
Laporotomy	Peak immediately post-op and decline to baseline within 72 hours[1]
Major abdominal surgery	Peak values: 30 mcg/dL[11]
Multiple trauma	Levels remain greater than 30 mcg/dL for a least a week;[12] peak values 40 to 50 mcg/dL; correlate with severity of injury[13]
Myocardial infarction (MI)	Peak within 8 hours post-MI; peak levels correlate with size of infarct[14-18]

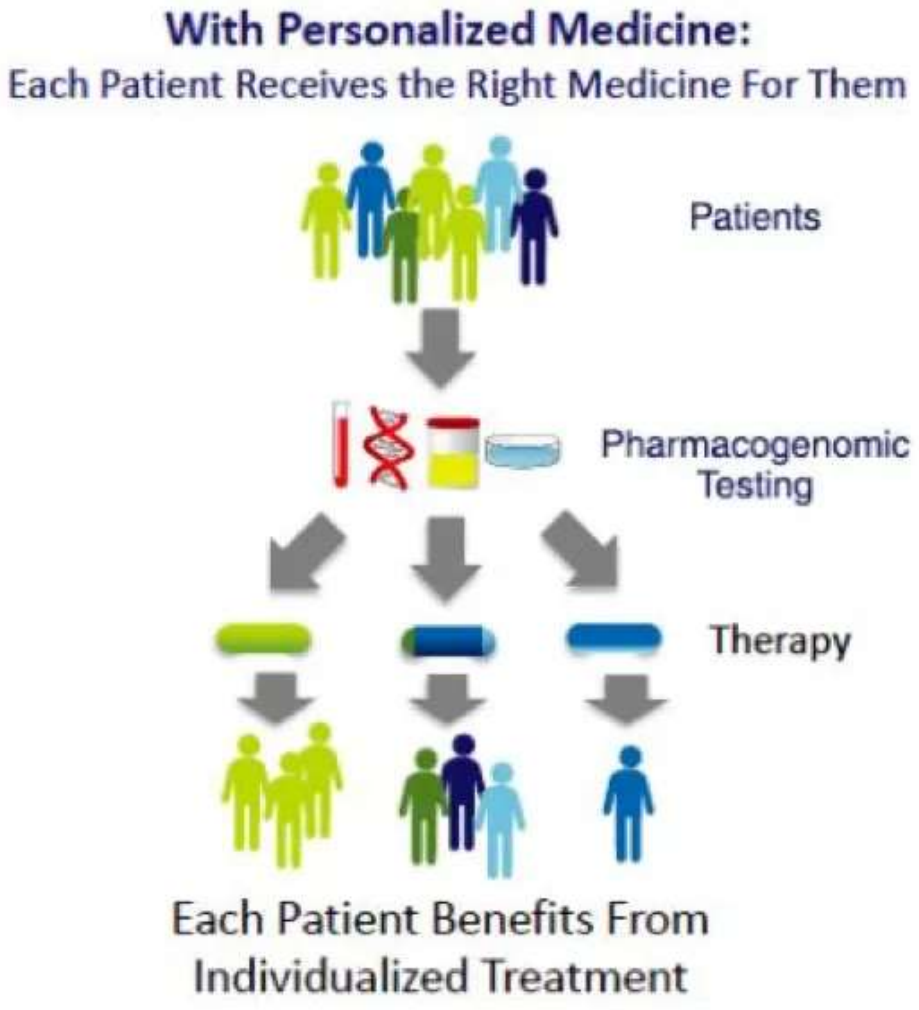
Jung C & Inder W 2008; MJA 188: 409-413

Take Home Messages

- **La terapia steroidea deve essere personalizzata il più possibile** considerando le caratteristiche della patologia da trattare, le caratteristiche del paziente e la presenza di fattori di rischio pre-esistenti.
- **Tutti gli steroidi con attività glucocorticoidea** possono causare la sindrome di Cushing e/o l'insufficienza surrenalica e/o la sindrome da carenza, di cui **non esistono predittori sicuri.**
- Occorre utilizzare la **minor dose** di glucocorticoide con la **maggior efficacia** terapeutica e per il **minor tempo** possibile.
- Non esistono evidenze circa l'efficacia e la sicurezza dei diversi **regimi di riduzione della terapia steroidea per garantire la ripresa dell'asse HPA** e tutti si basano su un **basso grado di evidenza**.

Medicina di precisione





Approcci interdisciplinari in reumatologia - 7ª edizione

MALATTIE REUMATICHE E DISORDINI ENDOCRINO-METABOLICI

Terapia steroidea personalizzata: possibilità e limiti

Grazie