70 ANNI DI REUMATOLOGIA ALLE MOLINETTE

Venerdì 11 ottobre 2019

SESSIONE III – MALATTIE REUMATICHE E METABOLISMO

Moderatori: M. Durazzo, P. Stobbione

Terapia steroidea cronica e asse ipofisi-surrene

Roberta Giordano

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Dip. Scienze Mediche; Università di Torino

Glucocorticoid treatment

… **widely used in clinical practice** (1-2% of the Western world, 3% in women older than 80 years) to control the activity of autoimmune, inflammatory, and allergic diseases, neoplasms of the hematopoietic system, and other diseases …

… administered through a **variety of routes** including oral, inhaled, nasal, topical, nasal, intra-articular, paratendinous or other soft tissue injections as well as systemic therapies…

… **Rheumatoid arthritis** …

(1948 Hench, 1995 "disease-modifying drugs, DMD") …

EULAR evidence-based recommendations on the management of systemic glucocorticoid therapy in rheumatic diseases

J N Hoes, J W G Jacobs, M Boers, D Boumpas, F Buttgereit, N Caeyers, E H Choy, M Cutolo, J A P Da Silva, G Esselens, L Guillevin, I Hafstrom, J R Kirwan, J Rovensky, A Russell, K G Saag, B Svensson, R Westhovens, H Zeidler, J W J Bijlsma

Ann Rheum Dis 2007;**66**:1560–1567. doi: 10.1136/ard.2007.072157

Low-dose
(≤ 7.5 mg/d prednisone)

EULAR evidence-based and consensus-based recommendations on the management of medium to high-dose glucocorticoid therapy in rheumatic diseases

Ann Rheum Dis 2013;**72**:1905–1913.

N Duru,[1] M C van der Goes,[1] J W G Jacobs,[1] T Andrews,[2] M Boers,[3] F Buttgereit,[4] N Caeyers,[5] M Cutolo,[6] S Halliday,[2] J A P Da Silva,[7] J R Kirwan,[8] D Ray,[9] J Rovensky,[10] G Severijns,[5] R Westhovens,[11] J W J Bijlsma[1]

Medium-high-dose
(>7.5 and ≤ 100 mg/d prednisone)

The **EULAR Glucocorticoid Task Force** has already published several recommendations over the last years such as those on the standardised 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.

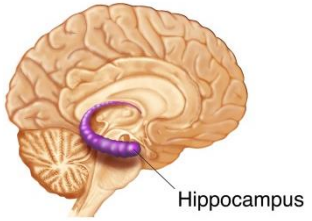
GC prescribed in conjunction with a maintenance treatment with early RA have proven to be symptomatically and structurally effective, even at low doses of 7.5 mg/d of prednisolone. Nonetheless, in light of the risk of long-term adverse events that increase with the cumulative dose, they should be prescribed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

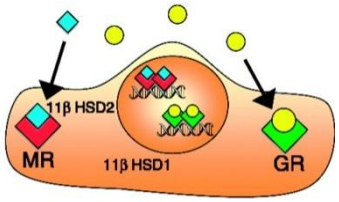
In light of the risks associated with cumulative doses of glucocorticoids, the most recent EULAR 2016 guidelines [32] recommend limiting the use of GC to when they are necessary, at the lowest dose possible, and for the shortest time possible (< 6 months). Glucocorticoids can also be recommended for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

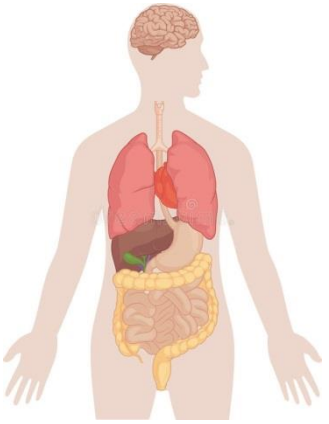
Initiation of long-term oral glucocorticoid therapy with early RA also exposes to a risk of self-medication and a "psychological" dependency, which are two factors that can compromise the chances of withdrawal after several months of treatment. The use of parenteral forms initially (IV or IM forms) as 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

MR - Glucocorticoid - GR



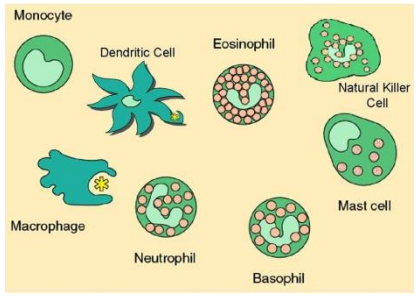




GC	Equivalent (replacement) doses (mg)	Anti-inflammatory potency (GR)	MR potency	T ½ (h)	Duration of action (h)
Short-acting					
Cortisone acetate	25	0.8	1.5	0.5	8-12
Hydrocortisone	20	1	2	1.5-2	8-12
Intermediate-acting					
Prednisone	**5**	4	1	1	18-36
Prednisolone	5	4	1	2-3.5	18-36
Methylprednisolone	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

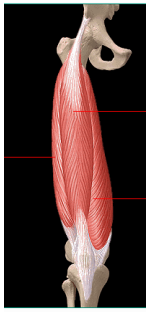
Glucocorticoid: biological effects

Immune system

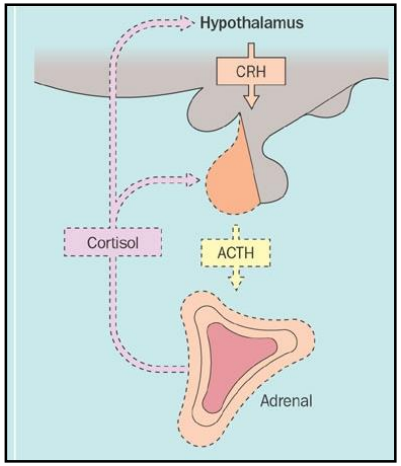


CNS

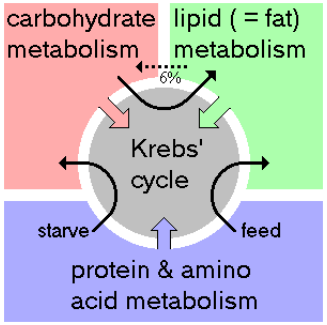
Muscle



HPA

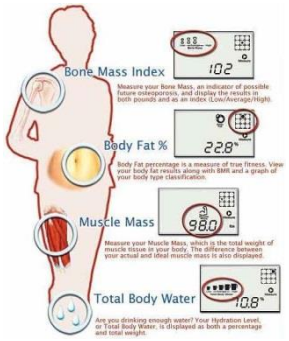


Energy metabolism

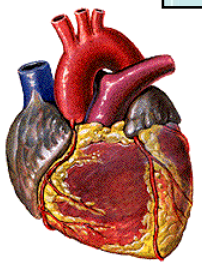


GC

Body composition



Bone metabolism



Cardiovascular system

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

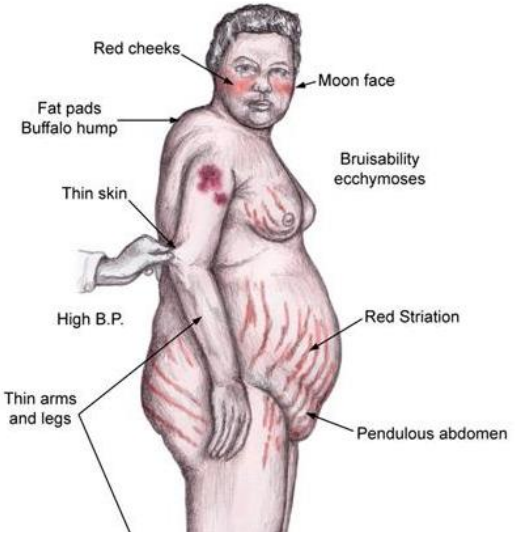
Risk of adrenal crisis

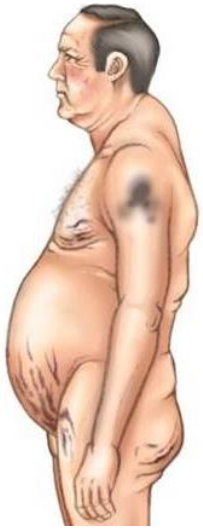
Paragliola RM et al., *Int J Mol Sci 2017; 18: 2201*

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 (> 5 mg/d of prednisone**) are usually required before patients manifest significant **Cushingoid effects**, **some patients**, in particular those on GCs following renal trnsplant, 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)

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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)

Asthma and Cushing's syndrome

Wilson AM *Chest 2000; 117: 593-594*

… **fluticasone propionate** = mometasonefuroate > budesonide = beclomethasone dipropionate > triamcinolone acetonide = flunisolide …
… **high doses** (0.75 mg/day for fluticasone propionate; 1.2-2.6 mg/day for budesonide, beclomethasone dipropionate)

Cushing's syndrome secondary to topical glucocorticoids

JoeE EK *Dermatol Online J 2003; 9:16-20*

… halobetasol propionate and betamethasone propionate for **6 months**….

Iatrogenic Cushing's syndrome due to nasal betamethasone: a problem not to be sniffed at!

Nutting CM *Postgrad Med J 1995; 71: 231-232*

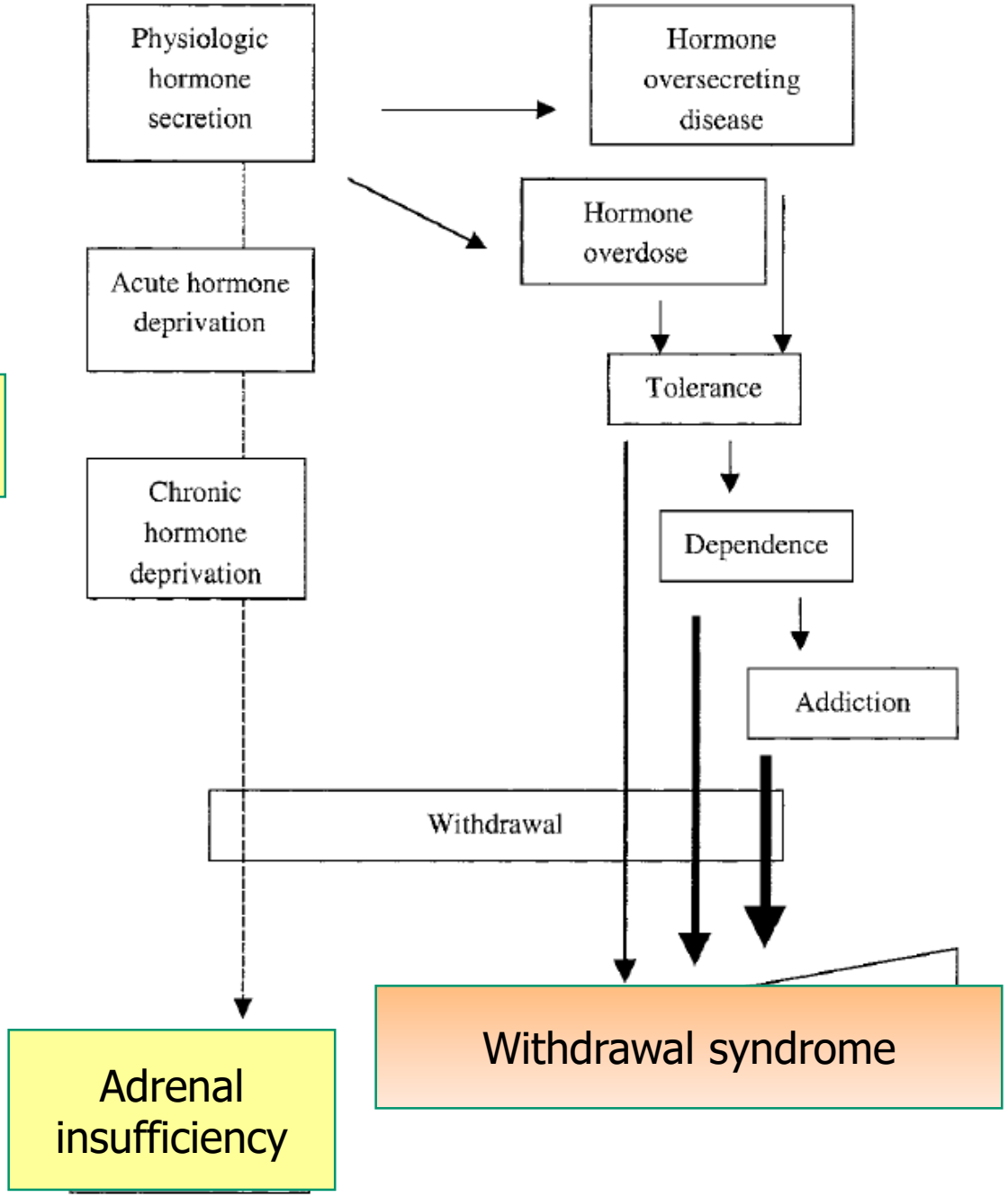
… betamethasone for **2 years**….

Four cases of secondary Cushingoid state following local triamcinolone acetonide (Kenacort) injection

Jansen TL et al. *Neth J Med 2002; 60: 151-153*

… triamcinolone acetomide **one local injection**….

Hormone deprivation



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

Adrenal insufficiency

… if GC are stopped suddenly in chronic users

… in acute situations (low doses)

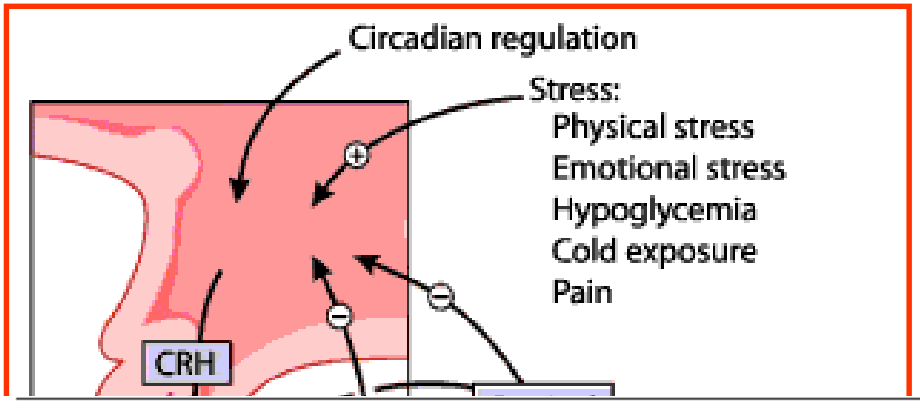
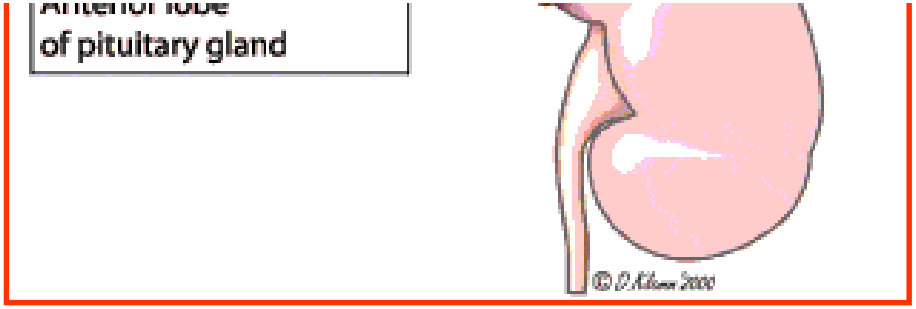


Table 3. The multi-dimensional nature of the so-called "stress response"

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)



… The exact dose and duration of treatment required for **significant HPA suppression vary between individuals …**

… **Some Authors ‘’feel’’ that oral GC treatment of less than 3 weeks duration** will **not lead HPA axis suppression**, no matter what the steroid dose, and therefore patients can be discontinued from steroid therapy immediately and safely up to that point.

… **Others believe** that at **high doses** (equivalent to oral **prednisone 20-30 mg day**), significant HPA suppression can occur after **as little as 5 days**, but that at **lower doses** (equivalent to oral **prednisone ≤7.5 mg day)**, suppression is unlikely to occurr **in less than 1 month.**

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

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

Department of Clinical Epidemiology (L.H.A.B., O.M.D.), Leiden University Medical Centre, Leiden 2300RC, The Netherlands; Department of Medicine (L.H.A.B., A.M.P., O.M.D.), Division of Endocrinology, Leiden University Medical Centre, Leiden 2300RC, The Netherlands; Department of Endocrinology (J.O.L.J., O.M.D.), Aarhus University, 8000 Aarhus C, Denmark; and Department of Clinical Epidemiology (O.M.D.), Aarhus University, 8000 Aarhus C, Denmark

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

Rebecca M. Joseph, MSc[a], Ann Louise Hunter, MBChB, MRCP[b], David W. Ray, MBChB, FRCP, PhD[b], William G. Dixon, MRCP, PhD[c,*]

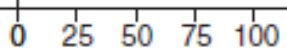
[a] *NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester University Hospitals NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK*
[b] *Manchester Centre for Endocrinology and Diabetes, Institute of Human Development, The University of Manchester, Manchester Academic Health Science Centre, Manchester, UK*
[c] *Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, Institute of Inflammation and Repair, The University of Manchester, Manchester Academic Health Science Centre, Manchester, UK*

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

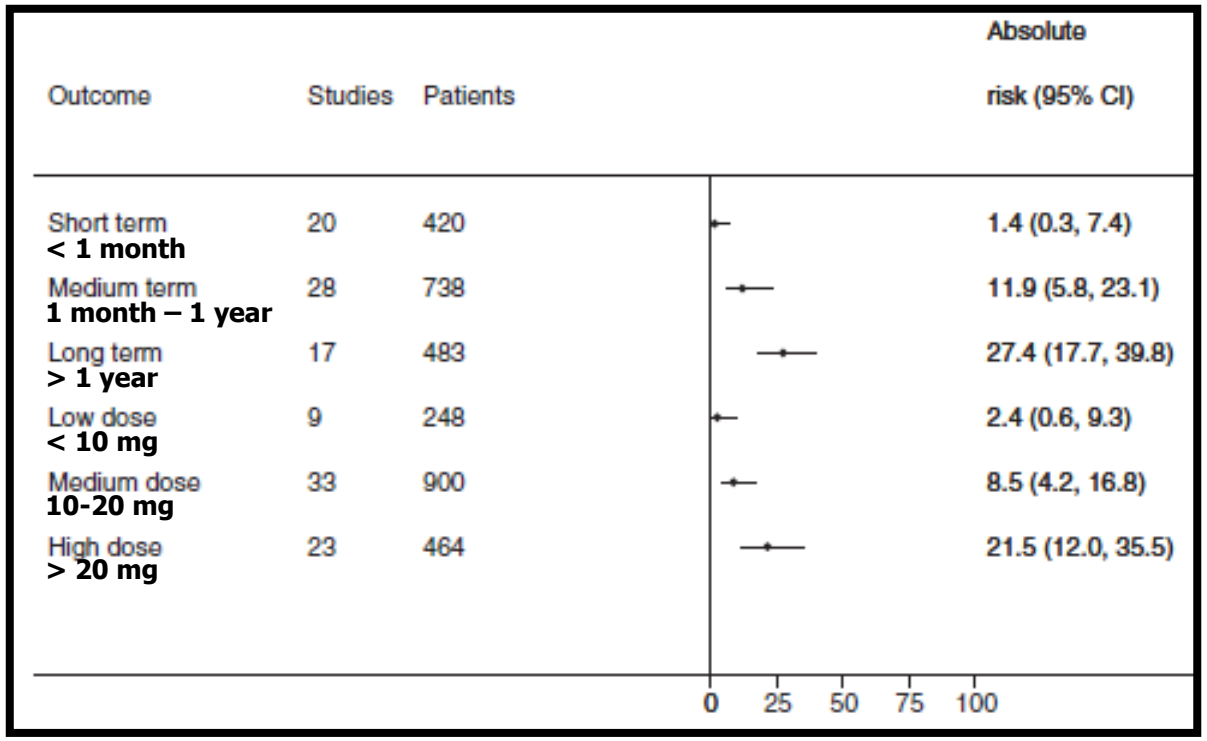
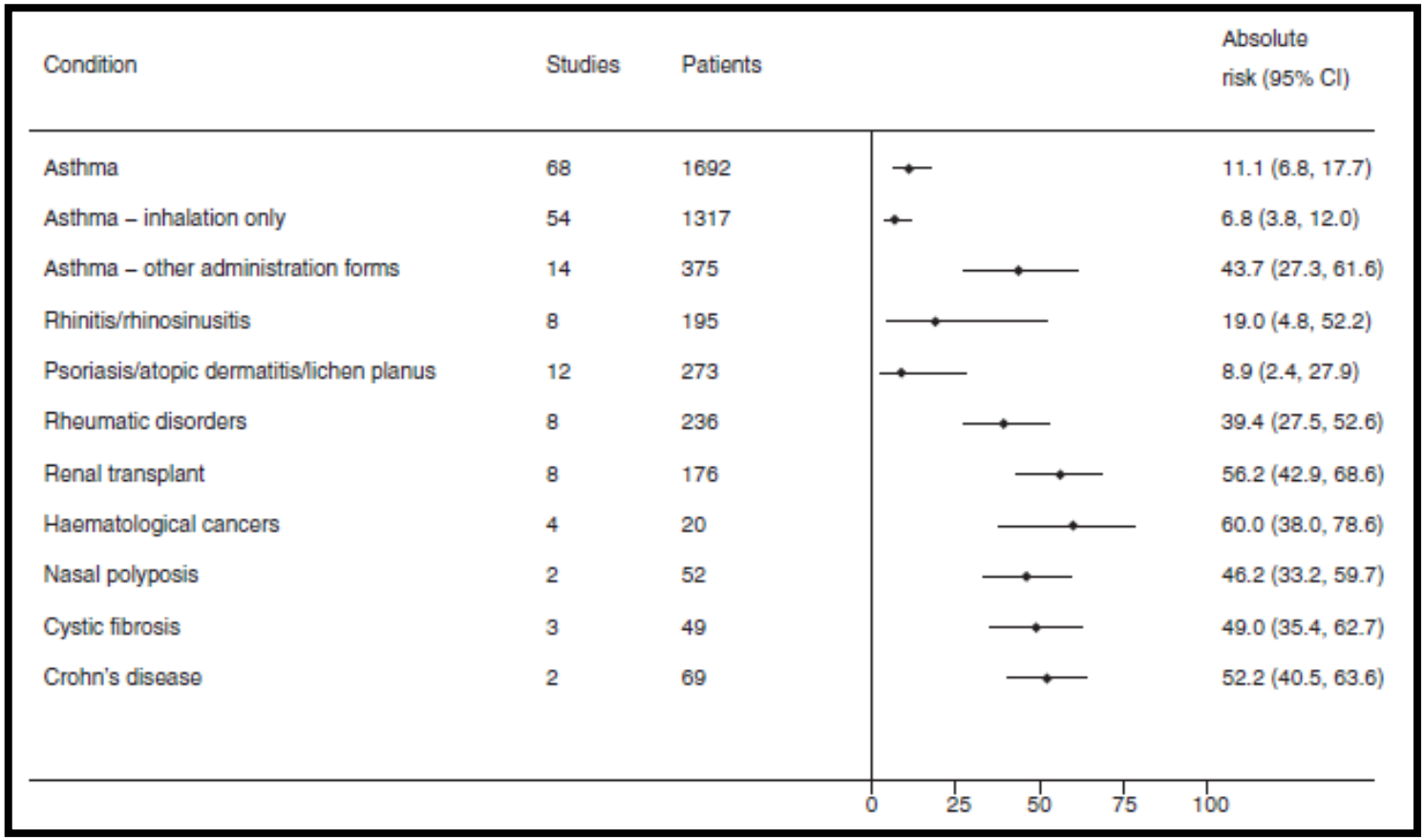


Table 3
Percentage of patients per group with AI by glucocorticoid dose, duration or cumulative dose.

	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



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

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>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

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

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[c]	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)

Clinical presentation

Table 1. Features Suggesting Corticosteroid Insufficiency.

Symptoms
Weakness and fatigue
Anorexia, nausea, vomiting
Abdominal pain
Myalgia or arthralgia
Postural dizziness
Craving for salt
Headaches
Memory impairment
Depression

Findings on physical examination
Increased pigmentation
Hypotension (postural)
Tachycardia
Fever
Decreased body hair
Vitiligo

Clinical problems
Hemodynamic instability
- Hyperdynamic (common)
- Hypodynamic (rare)

Ongoing inflammation with no obvious source
Multiple-organ dysfunction
Hypoglycemia

Laboratory findings
Hyponatremia
Hyperkalemia
Hypoglycemia
Eosinophilia
Elevated thyrotropin levels

… diagnosis delayed …

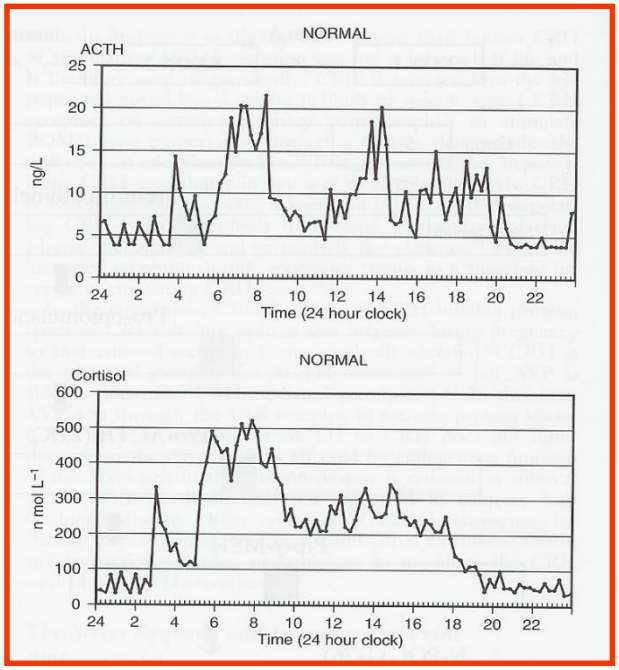
Diagnosis: How ?

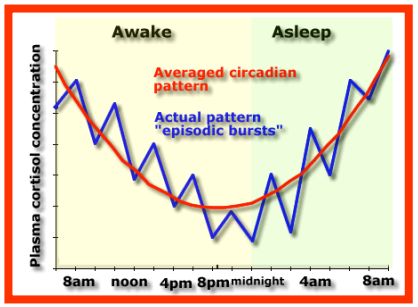
1. Baseline hormonal evaluation

Morning cortisol (h 7-9) "in unstressed patients"

Normality: > 15-18 µg/dl (400-500 nmol/l)

HPA-insufficiency:< 3-5 µg/dl (80-110 nmol/l)
(specificity 100%, low sensitivity)





Grinspoon & Biller 1994; JCEM 79: 923-931
Oelkers 1996; NEJM 335: 1206-1212
Courtney et al 2000; Clin Endocrinol 53: 431-436
Schmidt et al 2003; JCEM 88: 4193-4198
Arlt & Allolio 2003; Lancet 361: 1881-1893
Arlt 2009; JCEM 94: 1059-1067
Grossman 2010; JCEM 95: 4855-4863
Crowley et al 2014; JCEM 99: 4027-4036
Fleseriu M et al 2016; *JCEM 101:3888-3921*

2. Dynamic hormonal evaluation

Table 3. Dynamic Tests for Diagnosing Suspected Hypopituitarism

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

ACTH test 250 µg or 1 µg

… No single test is able to identify all patients … clinical judgement is decisive in the assessment, re-assessment and follow-up of these patients…

Diagnosis: When ?

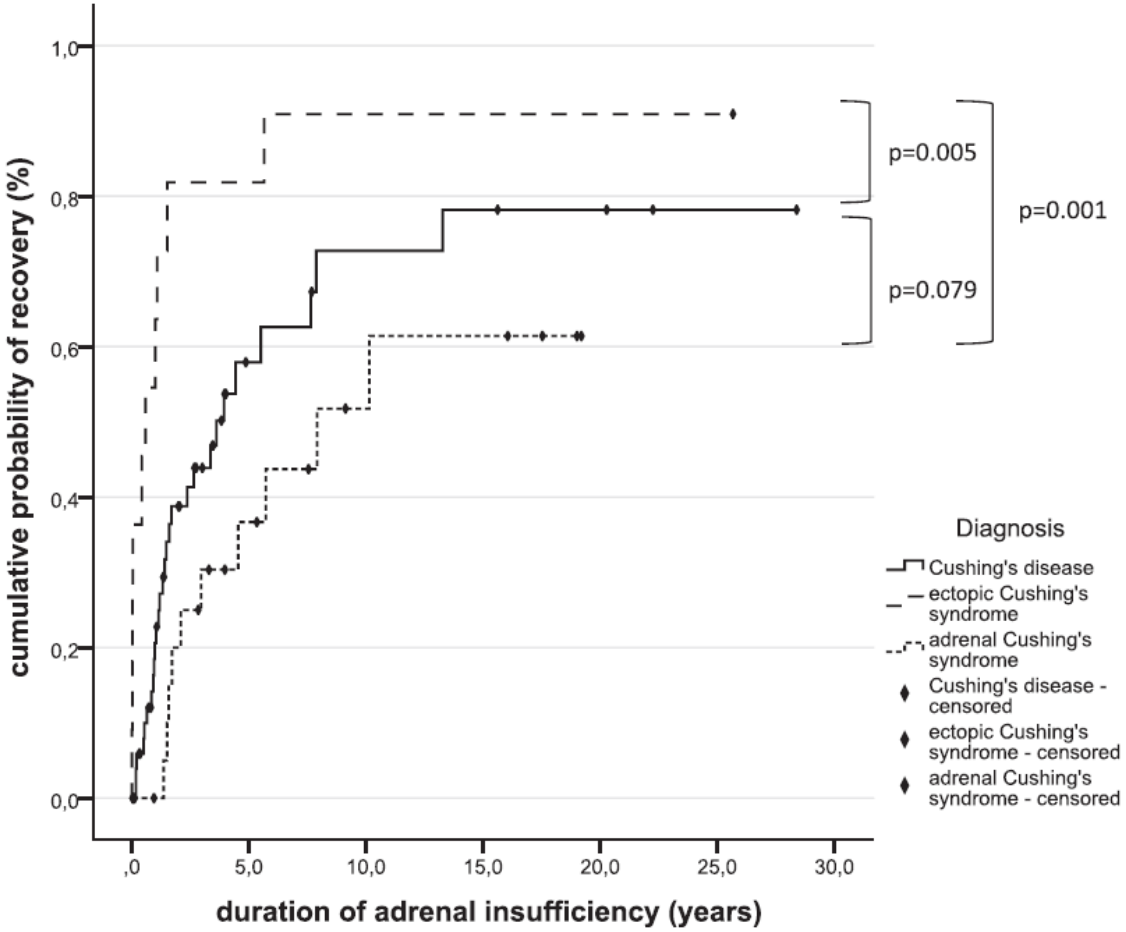
… We suggest that clinicians perform biochemical testing for the HPA axis **at least 18–24 hours after** the last HC dose or **longer** for synthetic GCs …

Fleseriu M et al 2016; *JCEM 101:3888-3921*

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

The effect of long-term glucocorticoid therapy on pituitary-adrenal responses to exogenous corticotropin-releasing hormone

Schlagheke R et al. *N Engl J Med 1992; 326: 226-230*

… 279 patients and 50 normal subjects …**5 to 30 mg of prednisone** for from 1 week to 15 years…
… **Neither dose, duration, nor basal plasma cortisol concentrations could be used reliably to predict pituitary-adrenal function …**

Suppression and recovery of adrenal response after short-term, high-dose glucocorticoid treatment

Henzen C. et al. *Lancet. 2000; 355:542-545*

… 75 patients… **25 mg prednisone daily** for between 5 days and 30 days..
… **There was no correlation between plasma cortisol concentrations and the duration or dose of glucocorticoid treatment …**

… **potency, dose and duration of GC use** are important but **imperfect predictors of HPA** suppression …

HPA-axis recovery

GC withdrawal syndrome

		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
3	**Psychological dependance**	

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

Adren ency

GC with drome

Tapering schedules

Stress-doses

Tapering schedules

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

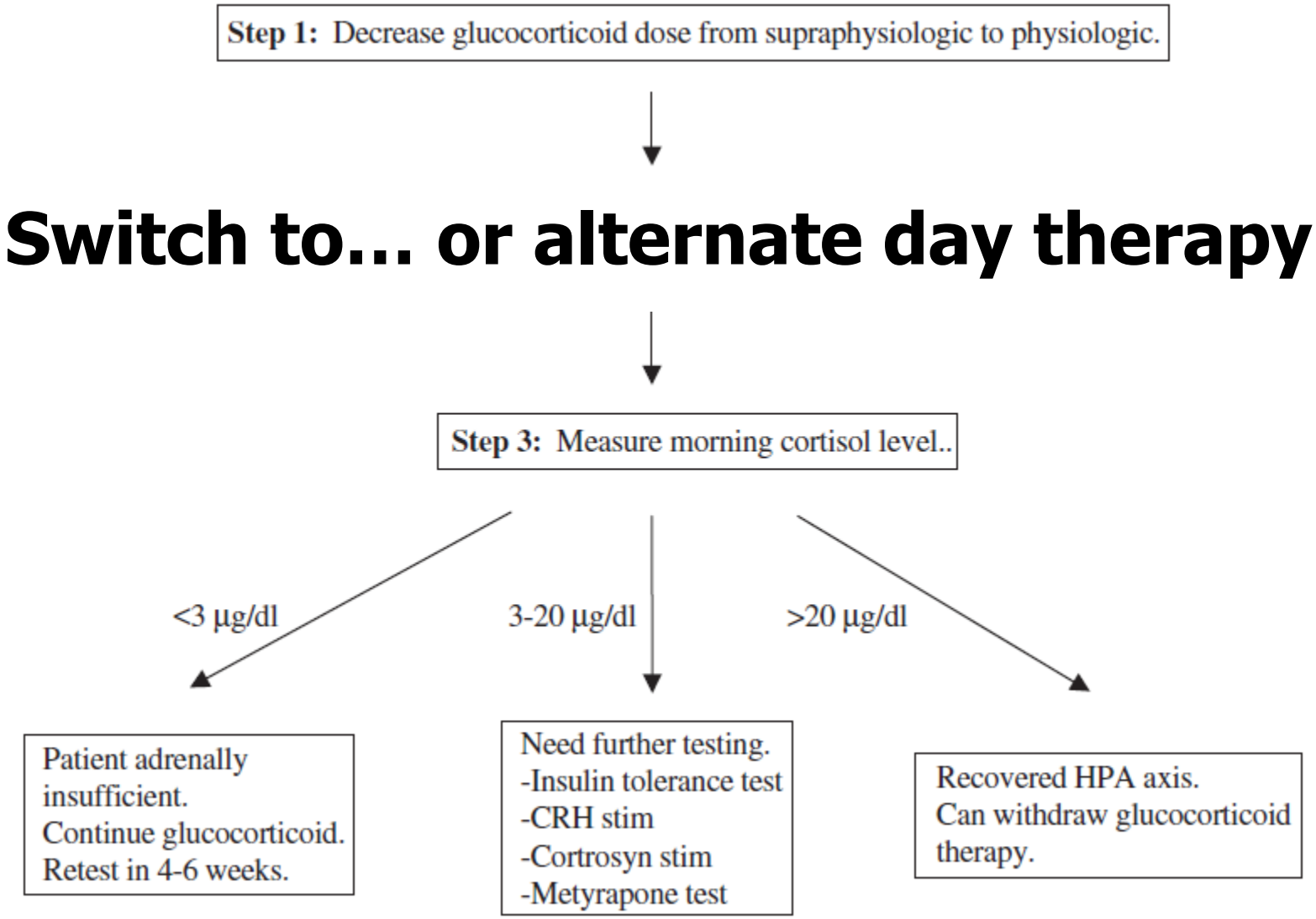
EULAR 2016-2017-2018

Prednisone or equivalent

Table 3 Recommended tapering schedules

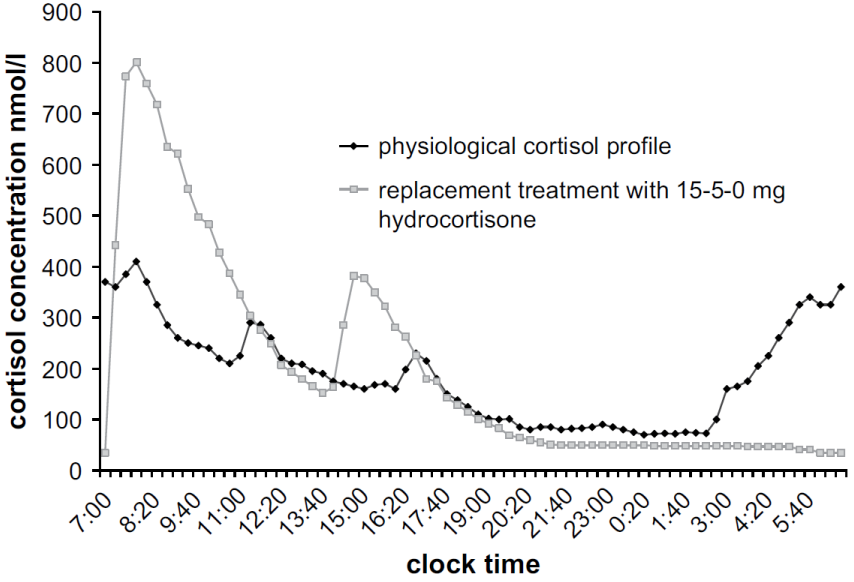
Starting dose of prednisone (or equivalent)	Progressive decrease of daily dose
>40 mg/day	5–10 mg/day every 1–2 weeks
20–40 mg/day	5 mg/day every 1–2 weeks
10–19 mg/day	2.5 mg/day every 2–3 weeks
5–9 mg/day	1 mg/day every 2–4 weeks
<5 mg/day	0.5 mg/day every 2–4 weeks

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

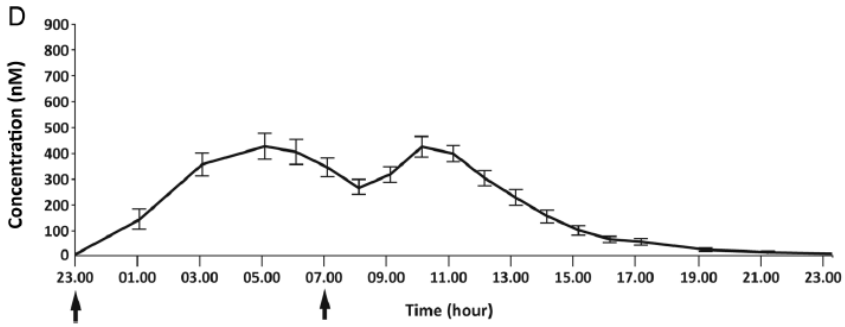


Hopkins RL et al., *Endocrinol Metab Clin N Am 2005; 34: 371-384*

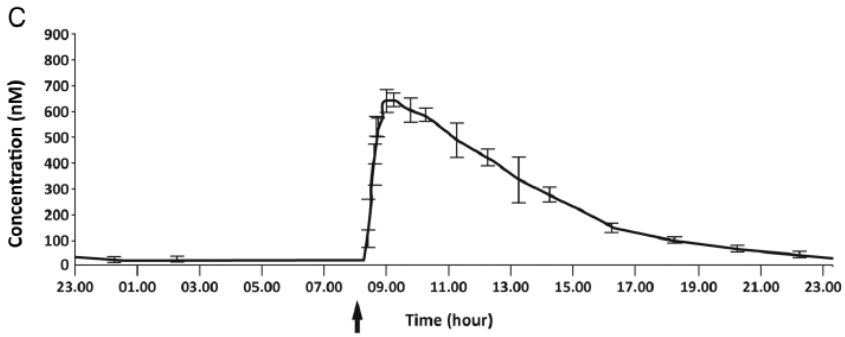
Switch to …



HC (10 mg)



CHRONOCORT



DR-HC
(Plenadren 5-20 mg)

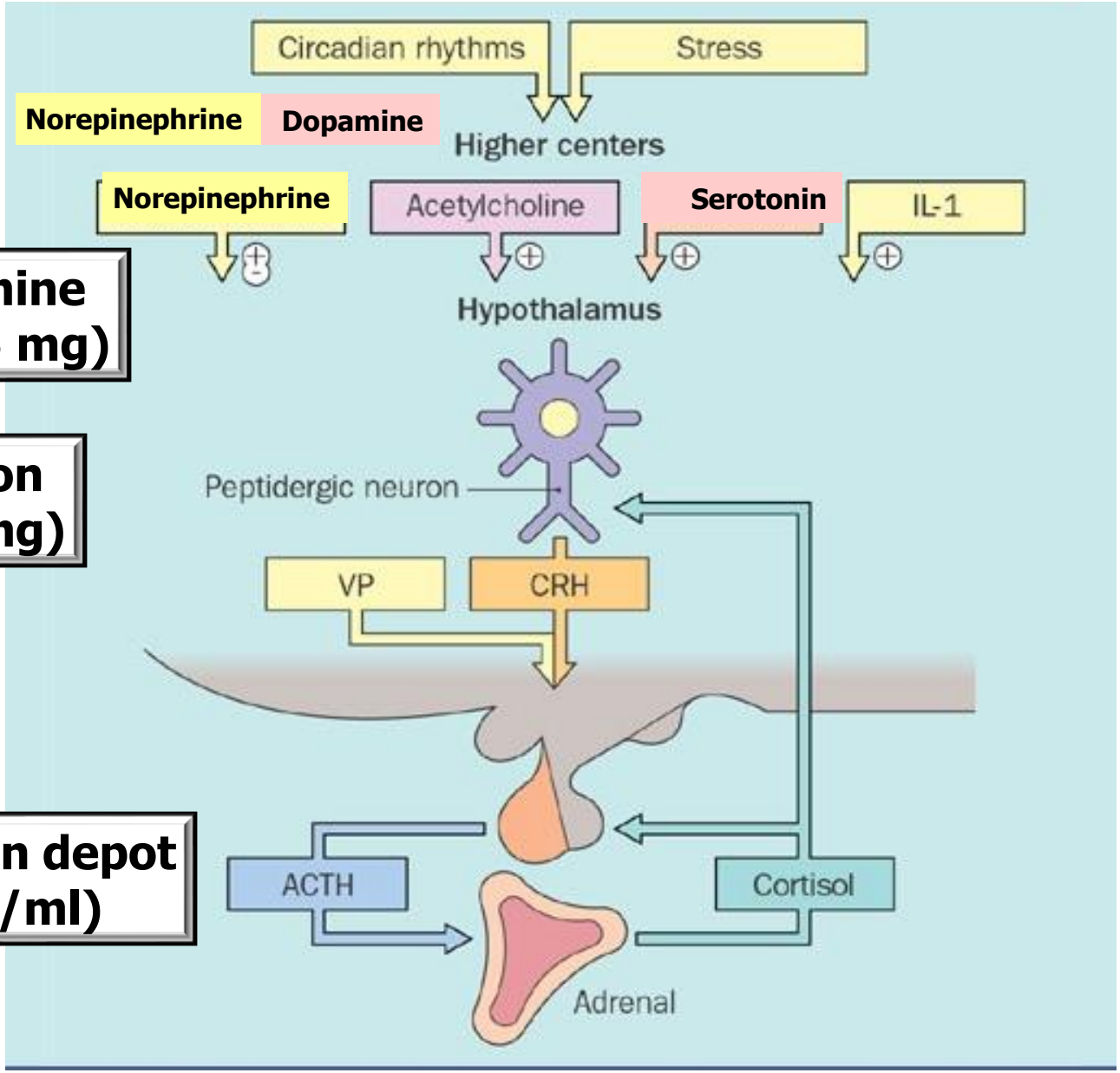
Porter J. et al. *Arch Dis Childh* 2017; 102: 199-2015

HPA-axis modulators ?

Sibutramine (cp 10-15 mg)

Bupropion (cp 150 mg)

Synacthen depot (1 mg/ml)



Stress-doses

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]

Table 3. Management of PAI in Specific Situations

Condition	Suggested Action
Home management of illness with fever	Hydrocortisone replacement doses doubled (>38°C) or tripled (>39°C) until recovery (usually 2 to 3 d); increased consumption of electrolyte-containing fluids as tolerated
Unable to tolerate oral medication due to gastroenteritis or trauma	Adults, im or sc hydrocortisone 100 mg; children, im hydrocortisone 50 mg/m^2 or estimate; infants, 25 mg; school-age children, 50 mg; adolescents, 100 mg
Minor to moderate surgical stress	Hydrocortisone, 25–75 mg/24 h (usually 1 to 2 d) Children, im hydrocortisone 50 mg/m^2 or hydrocortisone replacement doses doubled or tripled
Major surgery with general anesthesia, trauma, delivery, or disease that requires intensive care	Hydrocortisone, 100 mg per iv injection followed by continuous iv infusion of 200 mg hydrocortisone/24h (alternatively 50 mg every 6 h iv or im) Children, hydrocortisone 50 mg/m^2 iv followed by hydrocortisone 50–100 mg/m^2/d divided q 6 h

Borstein SR et al., *J Clin Endocrinol Metab. 2016;101:364-389*

Take Home Messages

- **Tutte le forme disponibili di steroidi con attività glucocorticoidea** possono causare la sindrome di Cushing e/o l'insufficienza surrenalica.
- Dal momento che **non esistono predittori** sicuri del rischio di sviluppare la sindrome di Cushing e/o l'insufficienza surrenalica, la **soglia** entro cui testare gli utilizzatori di glucocorticoidi dovrebbe essere **ampia nella pratica clinica**.
- Nessun singolo test ormonale è in grado di identificare correttamente tutti i pazienti con **insufficienza surrenalica**, mentre il giudizio clinico è decisivo nella valutazione, rivalutazione e nel follow-up dei pazienti sospetti.
- **La ripresa funzionale dell'asse HPA** richiede tempi diversi da caso a caso.
- Non esistono evidenze circa l'efficacia e la sicurezza dei diversi **regimi di riduzione della terapia steroidea** e tutti si basano su un **basso grado di evidenza**.

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