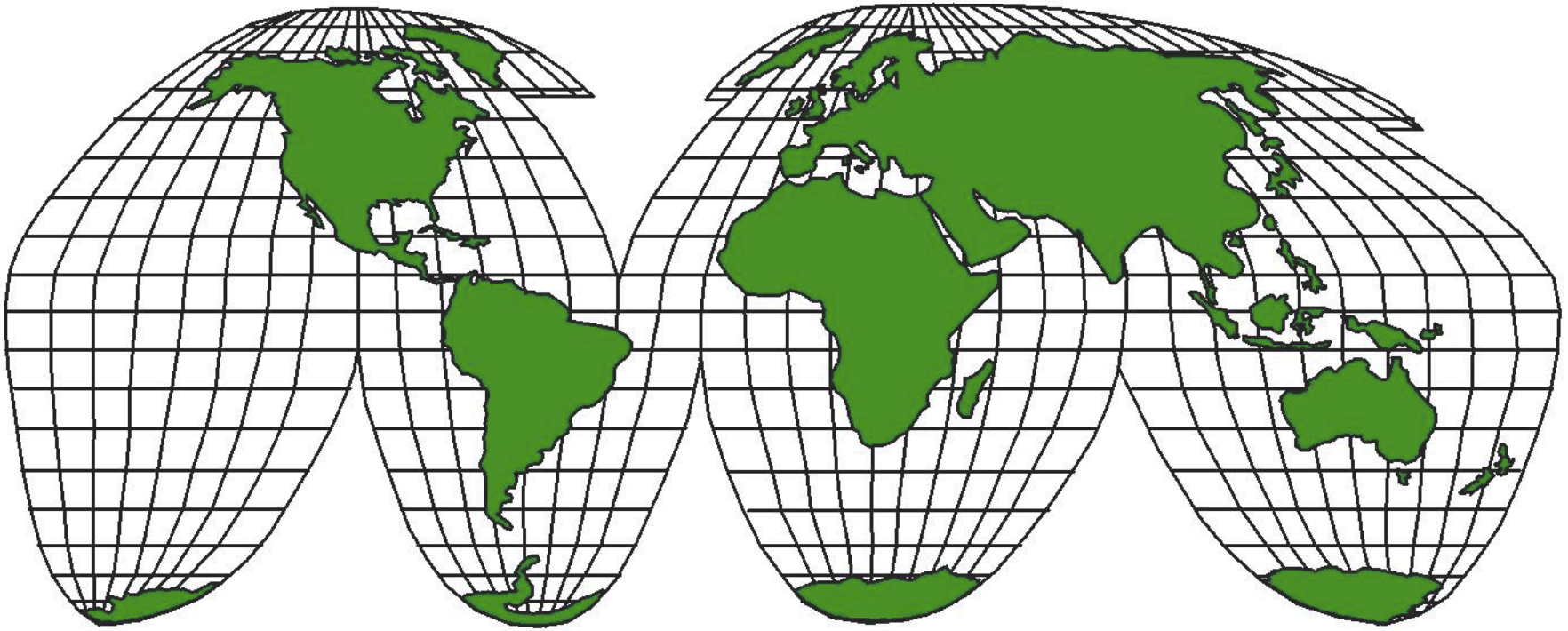
IPOSURRENALISMO

Francesco Scavuzzo
U.O. Endocrinologia
AORN "A.Cardarelli" Napoli

Epidemiologia della Malattia di Addison



In Europa:

Prevalenza:93-140 casi/milione

Incidenza:6.2 nuovi casi/milione/anno

In Italia si calcola che:

– esistano 6.000-7.000 casi

– compaiano 300 nuovi casi/anno

CAUSE DI MALATTIA DI ADDISON

• AUTOIMMUNI	75-80%
• Tubercolosi	15-17%
• Altre cause	2-5%

Definizione e tipologie di insufficienza surrenalica

AI primitiva (morbo di Addison)

- Causata dalla **distruzione o disfunzione della ghiandola surrenale**
- Prevalenza: 93–140 per milione
- Età di picco delle diagnosi: 4ª decade
- Deficit di glucocorticoidi e mineralcorticoidi

AI secondaria (Ipopituitarismo)

- Causata principalmente da **tumori ipotalamici/ipofisari**
- Prevalenza: 150–280 per milione
- Età di picco delle diagnosi: 6ª decade
- Deficit di glucocorticoidi (non mineralcorticoidi)
- Possono avere deficit multipli di ormoni ipofisari[3]

- L'**AI terziaria** può insorgere a seguito di una brusca interruzione del trattamento terapeutico (periodo prolungato) con steroidi ad alte dosi[4]

1. Arlt W. In: Harrison's Principles of Internal Medicine, 18th ed. 2012. Chapter 342, pp. 2940–2961
2. Artl W and Allolio B. Lancet 2003;361:1881–1893
3. Regal M et al. Clin Endocrinol 2001;55:735–740
4. Falorni A. et al. Endocrine 2012; 43 (3): 512-28

Segni/sintomi	Causa
Iperpigmentazione cute e mucose	**Stimolazione ACTH (POMC) – Ipocortisolismo primitivo**
Pallore cute	**Deficit ACTH (POMC) – Ipocortisolismo secondario**
Astenia, adinamia	**Deficit glucocorticoidi**
Riduzione appetito, peso	
Nausea, vomito	
Mialgia, dolori articolari	
Ipotensione	**Deficit mineralcorticoidi – Ipocortisolismo primitivo**
Ipotonia, ipovolemia	
Fame di sale	
Perdita peluria ascellare e pubica (femmine)	**Deficit androgeni**
Cute secca (femmine)	
Depressione, riduzione libido (femmine)	

Alterazioni ematochimiche	Cause
Iponatriemia 90% esordio	**Deficit glucococorticoidi, no inibizione secrezione ADH**
Iponatriemia/iperkaliemia	**Deficit mineralcorticoidi – Ipocortisolismo primitivo**
Ipokaliemia e alcalosi	**Vomito**
Ipercalcemia moderata 15%	**Deficit glucocorticoidi**
Anemia, linfocitosi, eosinofilia	
Ipoglicemia, neuroglucopenia	
Aumento azotemia e creatinina	**Deficit mineralcorticoidi – Ipocortisolismo primitivo**

L'insufficienza surrenalica è generalmente diagnosticata in ritardo[1]

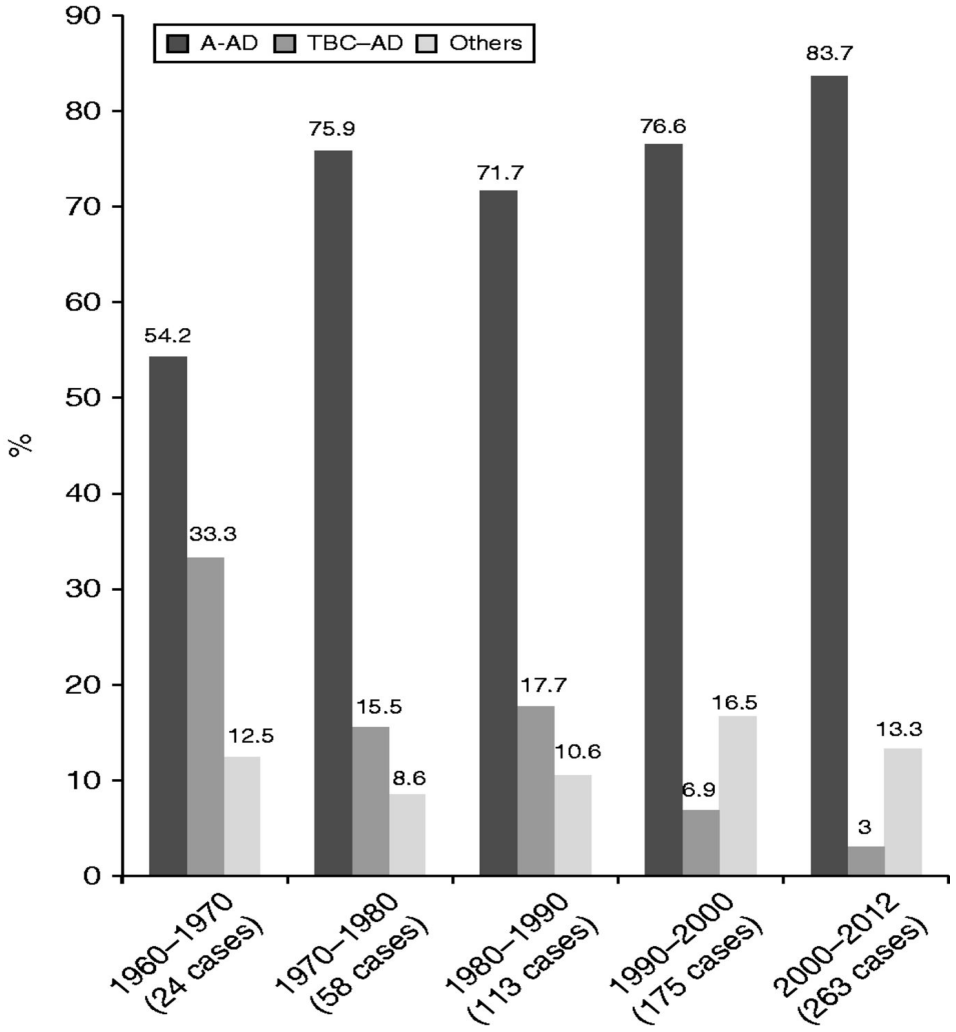
- <50% dei pazienti ricevono la diagnosi prima di un anno
- 67% dei pazienti ha consultato ≥3 medici prima di ricevere una diagnosi corretta
- 68% dei pazienti ha ricevuto inizialmente una diagnosi sbagliata
  - Le più comuni sono patologie psichiatriche e gastrointestinali

1. Bleicken B et al. Am J Med Sci 2010;339:525–531

Aetiology	Pathogenesis	Diagnosis
Autoimmune	T and B cell autoimmunity against adrenocortical cells	21OH-Ab
Infection	Mycobacteria Bacteria (e.g. meningococcus and Haemopholus influenzae) Fungus (e.g. *Pneumocystis carinii*) Virus (e.g. HIV, herpes simplex and cytomegalovirus)	Culture, Quantiferon test, PCR, adrenal CT
Bleeding	Antiphospholipid syndrome Anticoagulant therapy Disseminated intravascular coagulation	Evidence of bleeding on adrenal CT
Surgery	Tumour surgery, Cushing's syndrome, Radical nephrectomy	
Genetic	Congenital adrenal hyperplasia Adrenoleukodystrophy Hypogonadotrophic hypogonadism, Familiar glucocorticoid deficiency (ACTH resistance syndrome), Smith–Lemli–Opitz syndrome, mitochondrial forms (Kearns–Sayre syndrome)	Urine steroid profile, sequencing of steroidogenic genes (e.g. *CYP21B*) Measure VLCFA Sequencing of *NR0B1 (DAX1)*
Infiltrative	Amyloidosis, haemochromatosis, bilateral adrenal metastasis or lymphoma, xanthogranulomatosis	
Medication	Ketoconazole, etidomate, mitotane, metyrapone	

Husebye ES et al *J Int Med '14*

Figure 1 Frequencies of different forms of AD, diagnosed during the period from 1960 to 2012.



Corrado Betterle et al. Eur J Endocrinol 2013;169:773-784

Anticorpi	Metodiche di dosaggio
ACA	**Immunofluorescenza indiretta**
21-OHAbs	**RIA**

- Sindrome Polighiandolare Autoimmune (APS I) → 14.4%
  - Candidiasi cronica mucocutanea (18-100%)
  - Ipoparatiroidismo (22-93%)
  - Insufficienza corticosurrenalica (80-100%)

– Diabete mellito tipo 1	- Cheratocongiuntivite	- Alopecia
– Ipogonadismo ipergonadotropo	- Tiroidite	- Diarrea intrattabile
– Gastrite atrofica	- Nefrite interstiziale	- Insufficienza ovarica
– Anemia perniciosa	- Atrofia splenica	- Ipofisite
– Epatite cronica attiva	- Vitiligo	

- Mutaz
  - Transcription factor
  - Affects immune regulation

- Sindrome polighiandolare autoimmune tipo II (APSII) → 65.6%
  - ✧ Insufficienza surreenalica (100%)
  - ✧ Tiroidite autoimmune (69-82%)
  - ✧ Diabete mellito tipo 1 (30-52%)

- Vitiligo (4.5-11%)
- Gastrite cronica con anemia perniciosa (4.5-11%)
- Insufficienza ovarica
- Epatite cronica autoimmune (4%)
- Alopecia (1-4%)
- Miastenia gravis
- Ipofisite
- Celiachia

- ➢ **Associazione genetica aplotipi HLA A1, B8, DR3, DR4; polimorfismi gene CLTA4**

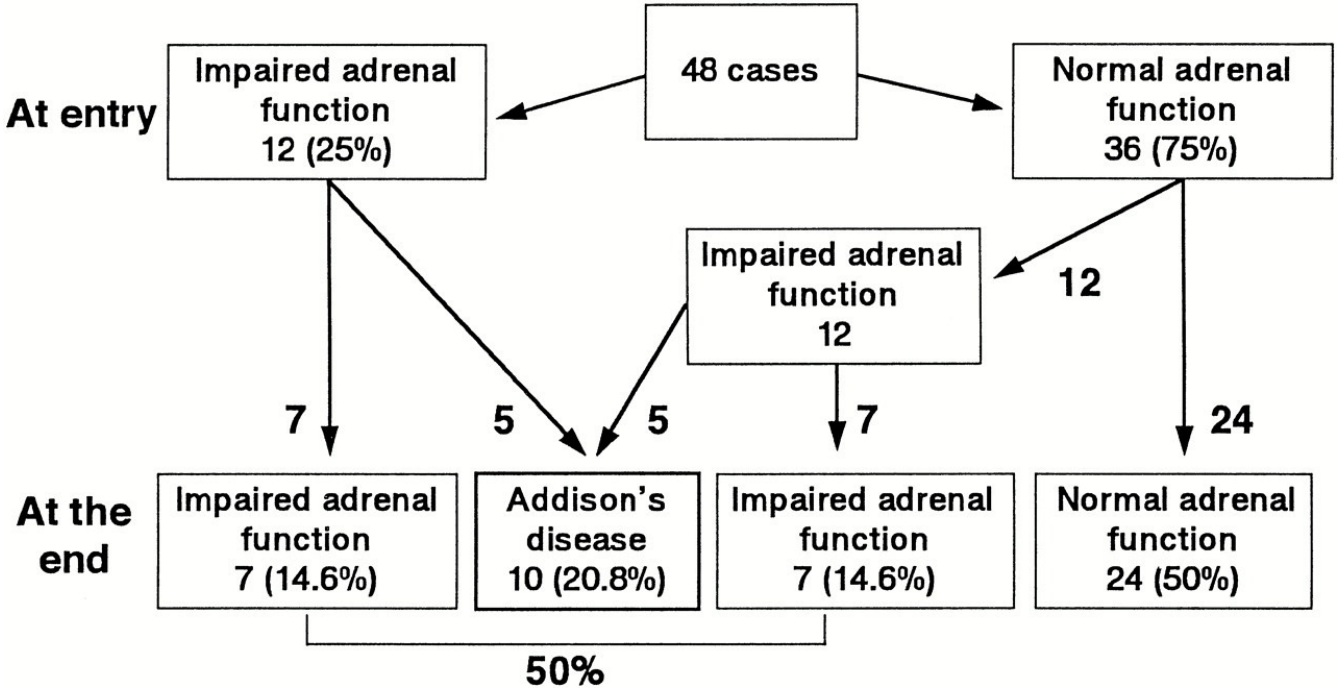


Figure 1. Follow-up of 48 polyendocrine non-Addisonian adult patients with adrenal cortex antibodies.

Published in: Corrado Betterle et al.,; *The Journal of Clinical Endocrinology & Metabolism* **1997,** 82, 932-938.
DOI: 10.1210/jcem.82.3.3819

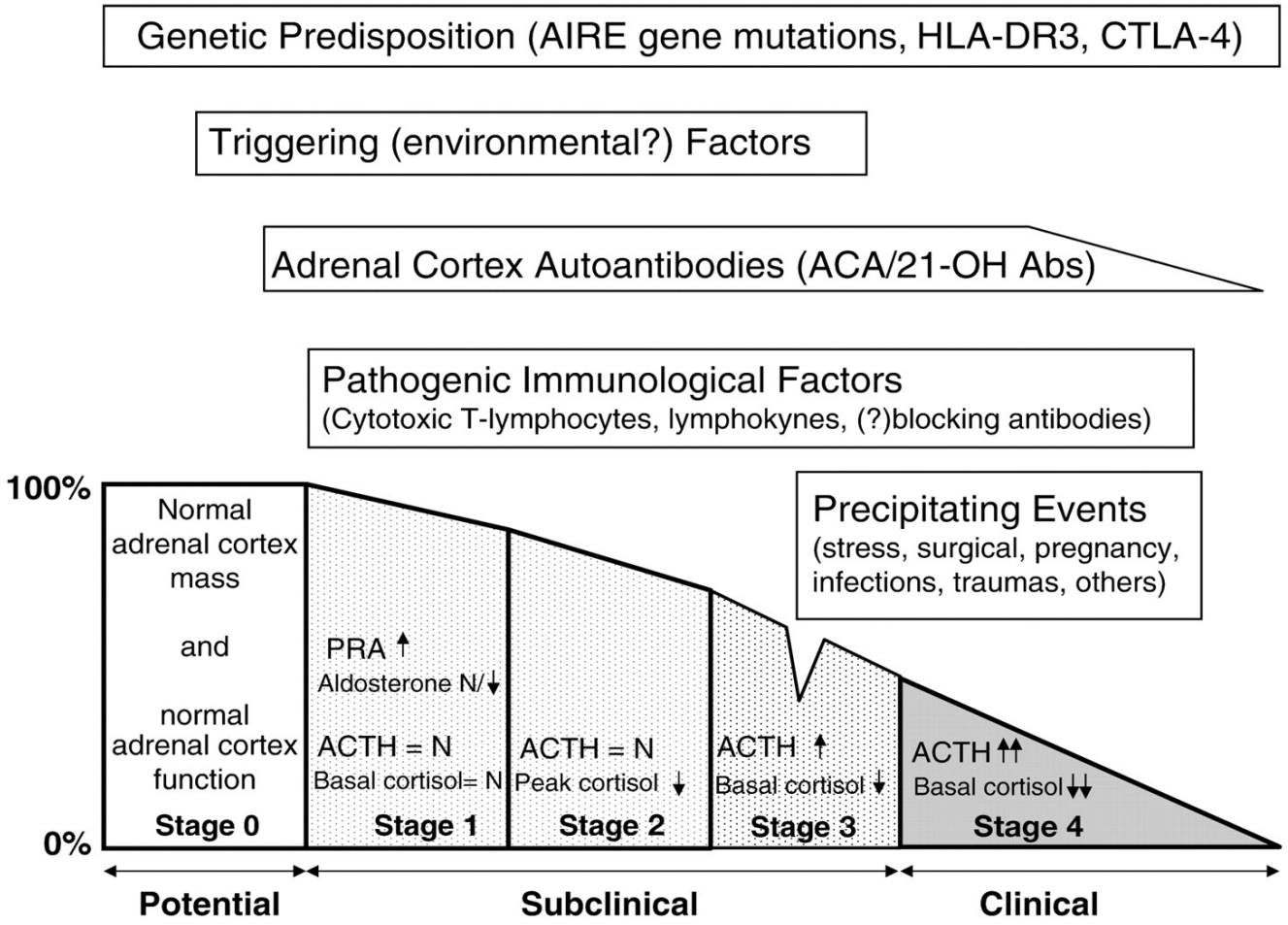


Figure 9. Natural history of autoimmune adrenalitis with the various stages of potential, subclinical, and clinical hypoadrenalism (see text for details) . N, Normal.

Published in: Corrado Betterle; Chiara Dal Pra; Franco Mantero; Renato Zanchetta; *Endocrine Reviews* **2002,** 23, 327-364.

Optimal diagnostic test

ACTH (Synachten) ev 250 mcg / 1 mcg	Tempi: 0', 30', 60'
Cortisolo	< 500/550 nmol/L; 18 mcg/dL

1 µg of an ACTH drug

Cortisolo tempi :o',30',60'(?)

Optimal diagnostic test

JClin Endocrinol Metab. 2016 Feb;101(2):427-34. doi: 10.1210/jc.2015-1700. Epub 2015 Dec 9.

ACTH Stimulation Tests for the Diagnosis of Adrenal Insufficiency: Systematic Review and Meta-Analysis.

Ospina NS[1], Al Nofal A[1], Bancos I[1], Javed A[1], Benkhadra K[1], Kapoor E[1], Lteif AN[1], Natt N[1], Murad MH[1].

For primary adrenal insufficiency, we included five studies enrolling 100 patients. Data were only available to estimate the sensitivity of high dose ACTH stimulation test (92%; 95% confidence interval, 81-97%).

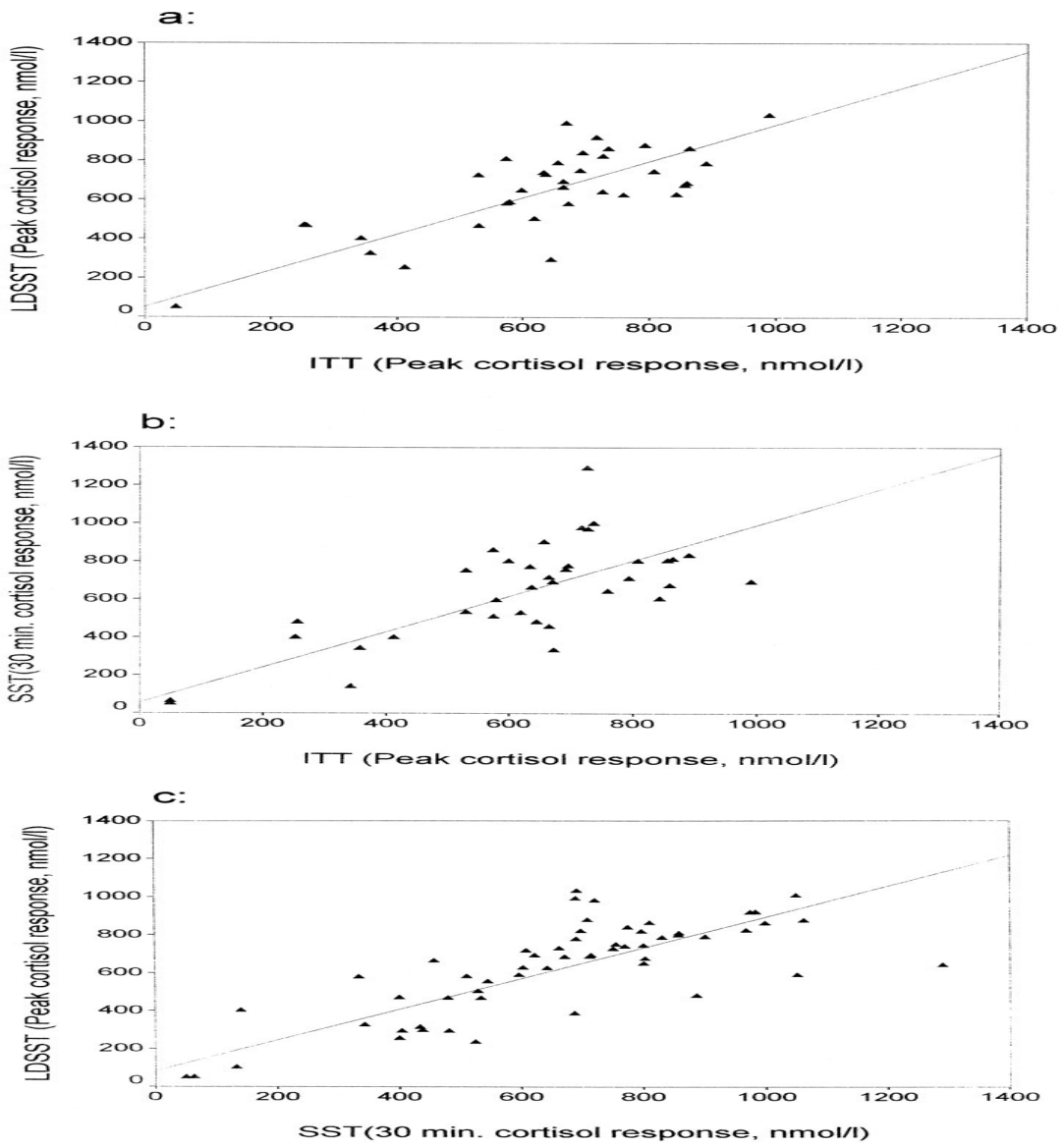
Optimal diagnostic test

Arch Dis Child. 2016 Mar 7. pii: archdischild-2015-308925.

A systematic review and meta-analysis of Synacthen tests for assessing hypothalamic-pituitary-adrenal insufficiency in children.

Ng SM[1], Agwu JC[2], Dwan K[3]

Lack of standardisation of assays and protocols with regard to timing, frequency and dose has resulted in diagnostic inaccuracies. There is no clear evidence to indicate that LDSST is superior to SSST in the assessment of HPA axis in children. The choice of either SSST or LDSST should be individualised based on clinical judgement for each patient. This systematic review has identified the need for a well-designed, adequately powered, randomised controlled trial on the use of diagnostic tests used in assessing HPA axis in children



Published in: T. A. M. Abdu; T. A. Elhadd; R. Neary; R. N. Clayton; *The Journal of Clinical Endocrinology & Metabolism* **1999,** 84, 838-843.
DOI: 10.1210/jcem.84.3.5535

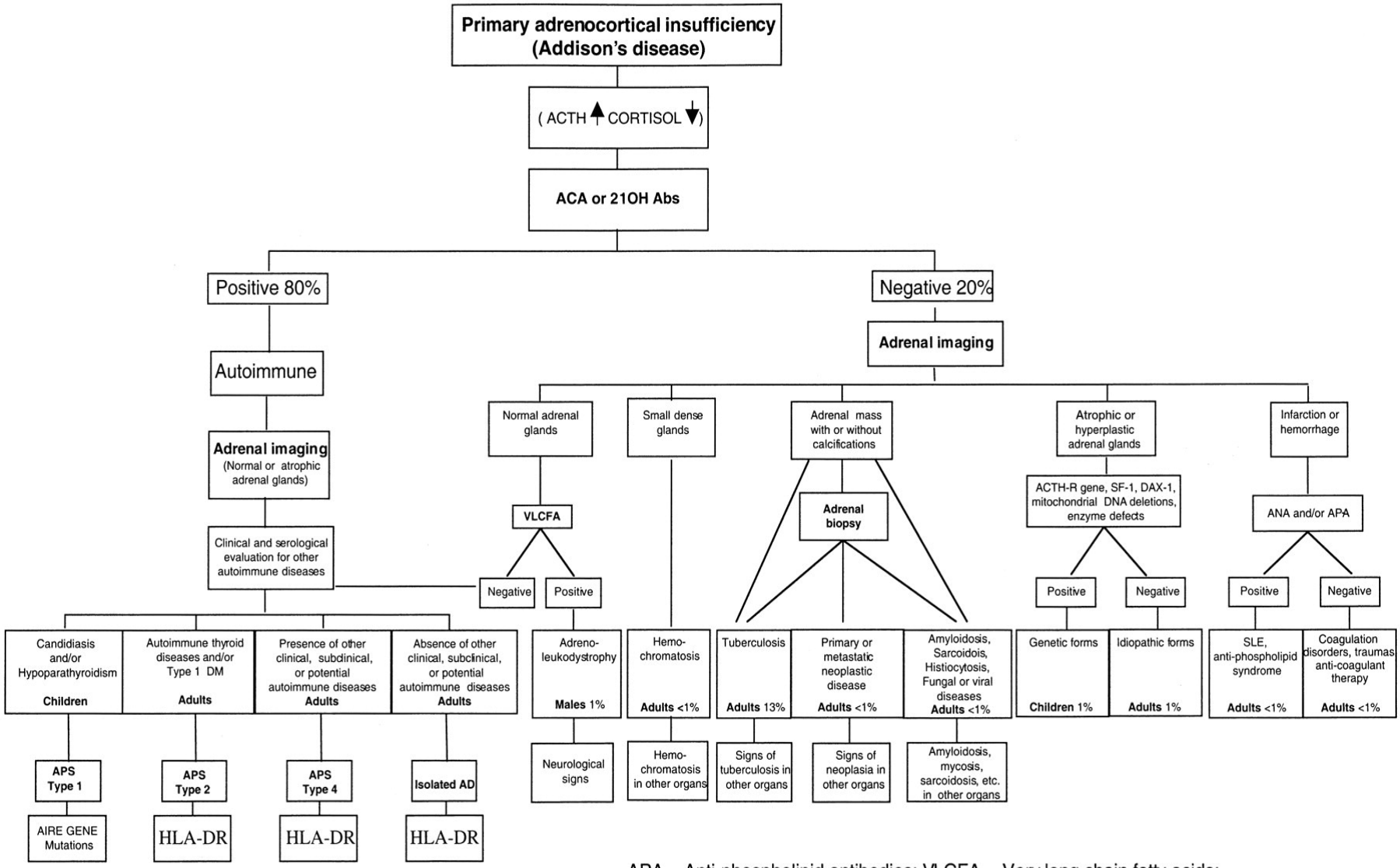
Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline

Stefan R. Bornstein (chair), Bruno Allolio, Wiebke Arlt, Andreas Barthel, Andrew Don-Wauchope, Gary D. Hammer, Eystein S. Husebye, Deborah P. Merke, M. Hassan Murad, Constantine A. Stratakis, and David J. Torpy*

2.0 Optimal diagnostic tests

2.1 We suggest the standard dose (250 μg for adults and children ≥2 y of age, 15 μg/kg for infants, and 125 μg for children <2 y of age) iv corticotropin stimulation (30 or 60 min) test over other existing diagnostics tests to establish the diagnosis of adrenal insufficiency. Peak cortisol levels below 500 nmol/L (18 μg/dL) (assay dependent) at 30 or 60 minutes indicate adrenal insufficiency. (2|⊕⊕◯◯)

2.2 We suggest the low-dose (1 μg) corticotropin test for diagnosis of PAI only when the substance itself is in short supply. (2|⊕⊕◯◯)



APA = Anti-phospholipid antibodies; VLCFA = Very long chain fatty acids;
ACA = Adrenal-cortex autoantibodies; 21-OH Abs = 21-Hydroxylase autoantibodies
ANA = Anti-nuclear antibodies; APS = Autoimmune Polyendocrine Syndrome

---

Published in: Corrado Betterle; Chiara Dal Pra; Franco Mantero; Renato Zanchetta; *Endocrine Reviews* **2002,** 23, 327-364.

Adrenal insufficiency: when and where to find it

Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline

Stefan R. Bornstein (chair), Bruno Allolio, Wiebke Arlt, Andreas Barthel, Andrew Don-Wauchope, Gary D. Hammer, Eystein S. Husebye, Deborah P. Merke, M. Hassan Murad, Constantine A. Stratakis, and David J. Torpy*

Table 2. Major Etiologies of PAI and Associated Features

Etiology	Associated Features
Autoimmune	
Isolated	Not associated with other autoimmune disorders
APS type 1 (APECED)	Chronic cutaneous candidiasis, hypoparathyroidism
APS type 2	Autoimmune thyroid disease, type 1 diabetes
Adrenal—infiltration/injury	
Adrenal hemorrhage	Associated with sepsis, anticoagulants, anti-cardiolipin/lupus anti-coagulant syndrome
Adrenal metastases	Malignancies: lung, breast, colon, melanoma, lymphoma
Infections: adrenalitis	Tuberculosis, HIV/AIDS, CMV, candidiasis, histoplasmosis, syphilis, African trypanosomiasis, paracoccidioidomycosis (eg, in South America)
Infiltration	Hemochromatosis, primary amyloidosis
Bilateral adrenalectomy	Procedure for intractable Cushing's syndrome or bilateral pheochromocytoma
CAH: most forms can cause salt loss	Commonest cause of PAI in children (80%); may be diagnosed in older individuals
21-Hydroxylase deficiency	Commonest type of CAH is 21-hydroxylase deficiency, with associated hyperandrogenism
11β-hydroxylase deficiency	Hyperandrogenism, hypertension (in older children and adults)
3β-hydroxysteroid dehydrogenase II deficiency	Ambiguous genitalia in boys, hyperandrogenism in girls
P450 side-chain cleavage deficiency (CYP11A1 mutations)	XY sex reversal
P450 oxidoreductase deficiency	Skeletal malformations, abnormal genitalia
Congenital lipoid adrenal hyperplasia (StAR mutations)	XY sex reversal
Adrenal hypoplasia congenita	X-linked NROB1, Xp21 deletion (with Duchenne's muscular deficiency), SF-1 mutations (XY sex reversal), IMAGe syndrome
ACTH insensitivity syndromes	Type 1: ACTH receptor, melanocortin 2 receptor gene MC2R Type 2: MRAP Familial glucocorticoid deficiency (MCM4, NNT, TXNRD2) TripleA (Allgrove's) syndrome, achalasia, Addison's disease, alacrima, AAAS gene mutation
Drug-induced	Adrenal enzyme inhibitors: mitotane, ketoconazole, metyrapone, etomidate, aminoglutethimide, drugs that may accelerate cortisol metabolism and induce adrenal insufficiency T_4 also accelerates cortisol metabolism (at least in part through stimulation of 11β-HSD2) CTLA-4 inhibitors may enhance autoimmunity and cause PAI
Other metabolic disorders	Mitochondrial disease (rare) Adrenoleukodystrophy in males Wolman's disease

Abbreviations: APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy; CMV, cytomegalovirus; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; CYP, cytochrome P; HSD, hydroxysteroid dehydrogenase; 11β-HSD2, 11β-hydroxysteroid dehydrogenase type 2; IMAGe, intrauterine growth restriction, metaphyseal dysplasia, adrenal hypoplasia congenital, genital abnormalities; MC2R, melanocortin 2 receptor gene; MCM4, minichromosome maintenance-deficient 4; MRAP, melanocortin receptor accessory protein; NNT, nicotinamide nucleotide transhydrogenase; StAR, steroidogenic acute regulatory protein; TXNRD2, thioredoxin reductase 2. [Derived from E. Charmandari E, et al: Adrenal insufficiency. *Lancet.* 2014;383:2152–2167 (164), with permission. © Elsevier.]

AI and Drugs

Exp Ther Med. 2016 May;11(5):1819-1822. Epub 2016 Mar 11.

Opioid endocrinopathy: A clinical problem in patients with cancer pain.

Merdin A[1], Merdin FA[1], Gündüz Ş[2], Bozcuk H[3], Coşkun HŞ[3]Ugeskr Laeger. 2016 Apr

Ugeskr Laeger. 2016 Apr 25;178(17)

Secondary adrenal insufficiency during opiate treatment.

Kornholt J

Hormonal status of the patients.

Hormone	Normal range	Hormone levels of patients, n (%)		
		Lower	Normal	Higher
TSH (n=20), μIU/ml	0.2–4.2	1 (5)	15 (75)	4 (20)
fT4 (n=19), pg/ml	0.9–1.7	1 (5.2)	18 (94.8)	0 (0)
ACTH (n=18), pg/ml	0–65	1 (5.5)	17 (94.5)	0 (0)
Cortisol (n=20), μg/dl	4.3–22.4	3 (15)	9 (45)	8 (40)
FSH (n=20), mIU/ml	Female: 3.5–12.5	6 (30)	5 (25)	9 (45)
	Male: 1.5–12.4			
LH (n=20), mIU/ml	Female: 2.4–12.6	6 (30)	6 (30)	8 (40)
	Male: 1.7–8.6			
Total testosterone (n=16), ng/ml	Male: 1.9–5.4	11 (68.7)	5 (31.3)	0 (0)
	Female: 0.06–0.8			
Free testosterone (n=14), pg/ml	Male: 4.9–21.6	8 (57.1)	6 (42.9)	0 (0)
	Female: 0–2.6			
GH (n=19), ng/ml	0–8	0 (0)	18 (94.8)	1 (5.2)
Estradiol (n=8), pg/ml	Female: 24–195	2 (25)	5 (62.5)	1 (12.5)
	Male: 13.5–59.5			
Prolactin (n=14, ng/ml	4.1–18.4	0 (0)	8 (57.1)	6 (42.9)

Opioid endocrinopathy: A clinical problem in patients with cancer pain

AI and Oncology

Oncology. 2016 Apr 13. [Epub ahead of print]
Assessment of Adrenal Function and Health-Related Quality of Life in Advanced Gastric Cancer Patients Who Received First-Line Chemotherapy.
Kim HR[1], Kim JH, Rhee Y, Lee H, Song SE, Kim C, Song S, Noh SH, Rha SY

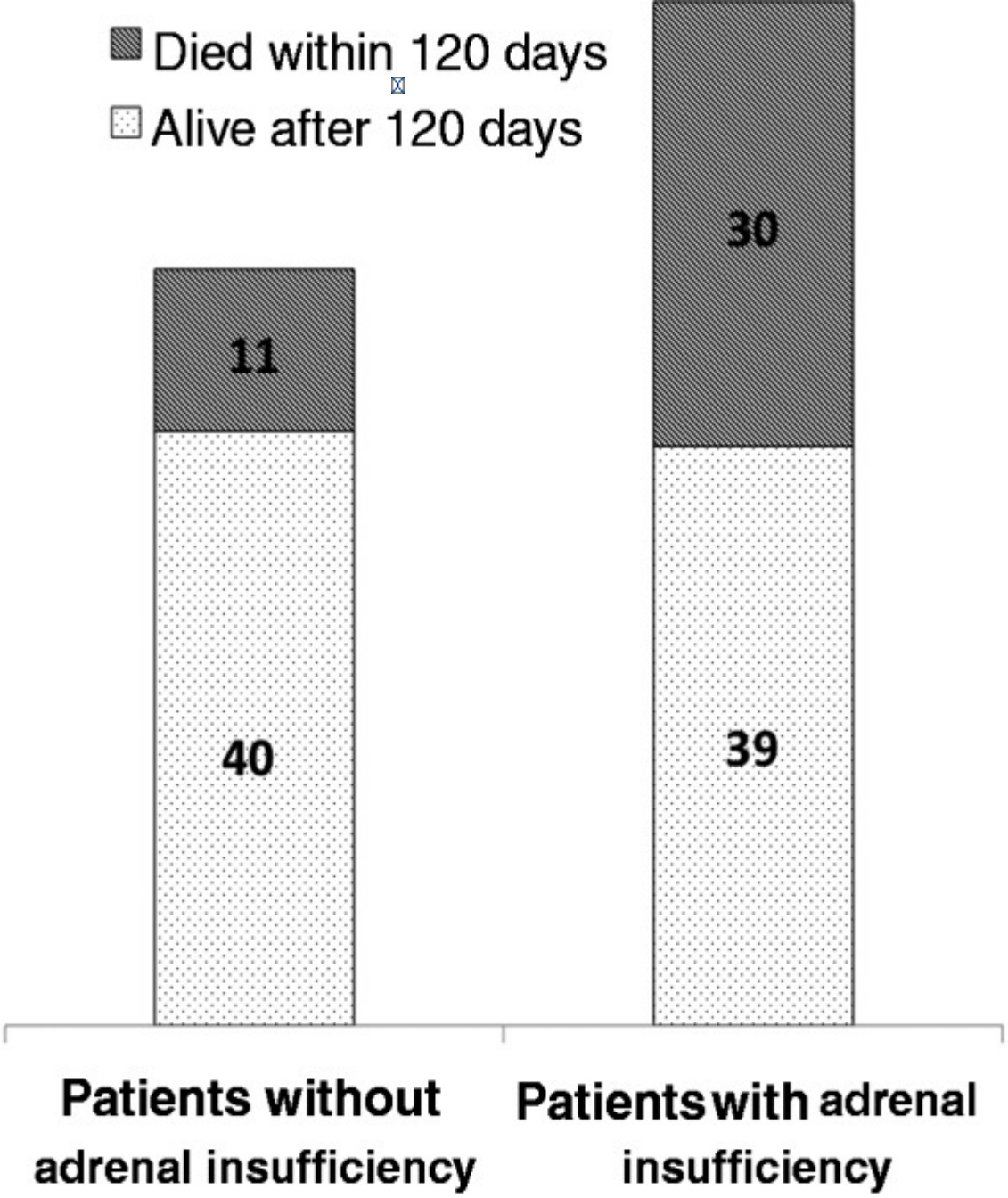
AI and Oncology

Future Oncol. 2016 Feb;12(3):413-25.
Risk of endocrine complications in cancer patients treated with immune check point inhibitors: a meta-analysis.
Abdel-Rahman O[1], ElHalawani H[1], Fouad M[2]

Curr Opin Oncol. 2016 Apr 28. [Epub ahead of print]
Endocrinological side-effects of immune checkpoint inhibitors.
Torino F[1], Corsello SM, Salvatori R.

CONCLUSION:
Our meta-analysis has demonstrated that the use of immune check point inhibitors is associated with an increased risk of hypothyroidism, hyperthyroidism, hypophysitis and adrenal insufficiency compared with control.

AI and cirrhosis



Outcome of patients with and without adrenal insufficiency.

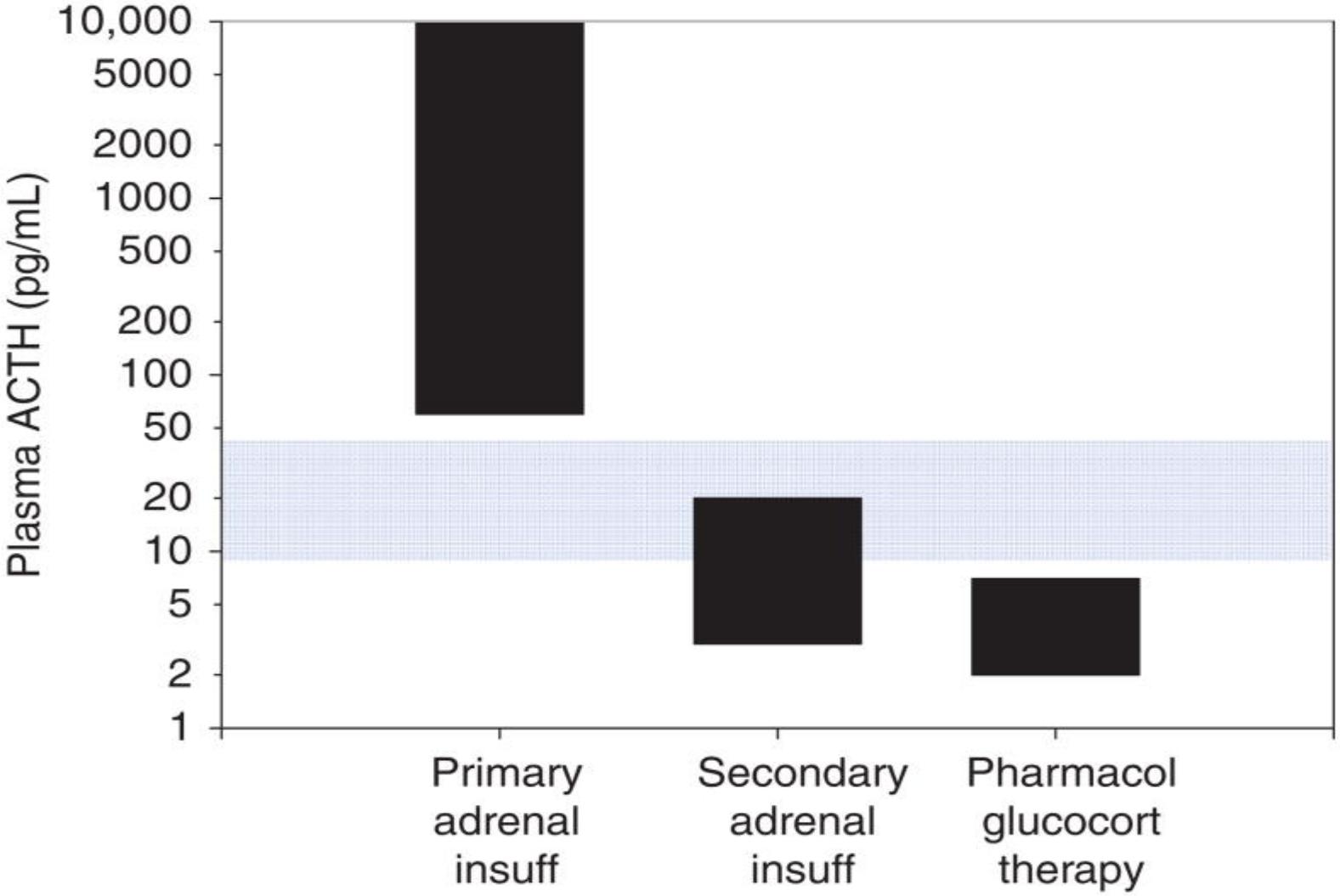
Adrenal insufficiency predicts early mortality in patients with cirrhosis

United European Gastroenterol J. 2015 December; 3(6):529-538

AI and cirrhosis

Prevalence of adrenal insufficiency in critically ill patients with liver cirrhosis

Ref.	No. of patients (type of cirrhosis)	Diagnosis and definition of AI	Prevalence of AI
Harry et al[14]	20 (ALF/CLD)	SD-SST: Peak cortisol < 500 nmol/L[1]	69%
Marik et al[12]	340 (ALF: 24)(CLD: 146)(recent LT: 119) (remote LT: 51)	LD-SST: Peak cortisol < 552 nmol/L orrandom cortisol level < 414 nmol/L in non-stressed patients orrandom cortisol level < 552 nmol/L in stressed patients	72%33%66% 92%61%
Tsai et al[8]	101 (cirrhosis+ severe sepsis)	SD-SST: Baseline cortisol < 414 nmol/L ordelta cortisol < 250 nmol/L if baseline cortisol between 414 and 938 nmol/L	51%
Fernandez et al [13]	25 (cirrhosis + septic shock)	SD-SST: Baseline cortisol < 414 nmol/L ordelta cortisol < 250 nmol/L if baseline cortisol between 414 and 966 nmol/L	68%
Thierry et al[64]	14 (cirrhosis + septic shock)	SD-SST: Baseline cortisol < 414 nmol/L; delta cortisol < 250 nmol/L	77%
du Cheyron et al [65]	50 (critically ill cirrhosis)	SD-SST: Baseline cortisol < 414 nmol/L; delta cortisol < 250 nmol/L if baseline cortisol between 414 and 938 nmol/L	82%
Vasu et al[86]	24 (critically ill cirrhotics)	SD-SST: Definition of AI was not reported	62%
Arabi et al[29]	75 (cirrhosis + septic shock)	SD-SST: Delta cortisol < 250 nmol/L	76%
Mohamed et al [85]	15 (cirrhosis+septic shock)	SD-SST: Definition of AI was not reported	87%
Thevenot et al [74]	30 (cirrhosis + sepsis)	SD-SST: Peak serum total cortisol < 510 nmol/L	10%
Acevedo et al [89]	166 (decompensated cirrhosis)	SD-SST: Delta cortisol < 250 nmol/L	26%
Graupera et al [20]	37 (severe acute bleeding)	SD-SST: Baseline cortisol < 414 nmol/L and/or delta cortisol < 250 nmol/L	38%
Triantos et al [16]	20 (cirrhosis with variceal bleeding)	SD-SST: Baseline cortisol < 276 nmol/L or delta cortisol < 250 nmol/LLD-SST: Peak serum cortisol < 690 nmol/L or a delta cortisol < 250 nmol/L	30%60%
El Damarawy et al[66]	45 (cirrhosis with septic shock or HRS, cirrhosis without septic shock or HRS)	SD-SST: Baseline cortisol < 414 nmol/L or delta cortisol < 250 nmol/L in patients with baseline cortisol < 966 nmol/L	73%



AI and Drugs

Physiological Basis for the Etiology, Diagnosis, and Treatment of Adrenal Disorders: Cushing's Syndrome, Adrenal Insufficiency, and Congenital Adrenal Hyperplasia

Compr Physiol. ;4(2):739-769.

AI and Drugs

In our retrospective study on the incidence, precipitating causes and risk factors of AC in Dutch patients with AI, we found an incidence rate of 52 AC/100 PY in PAI and 36 AC/100 PY in SAI as compared to 15.1 AC/100 PY in TAI (overall 41 AC/ 100 PY).

Clinical Endocrinology (2016) 84, 17–22 Incidence of adrenal crisis in patients with adrenal insufficiency
Lisanne C.C.J. Smans et al.,

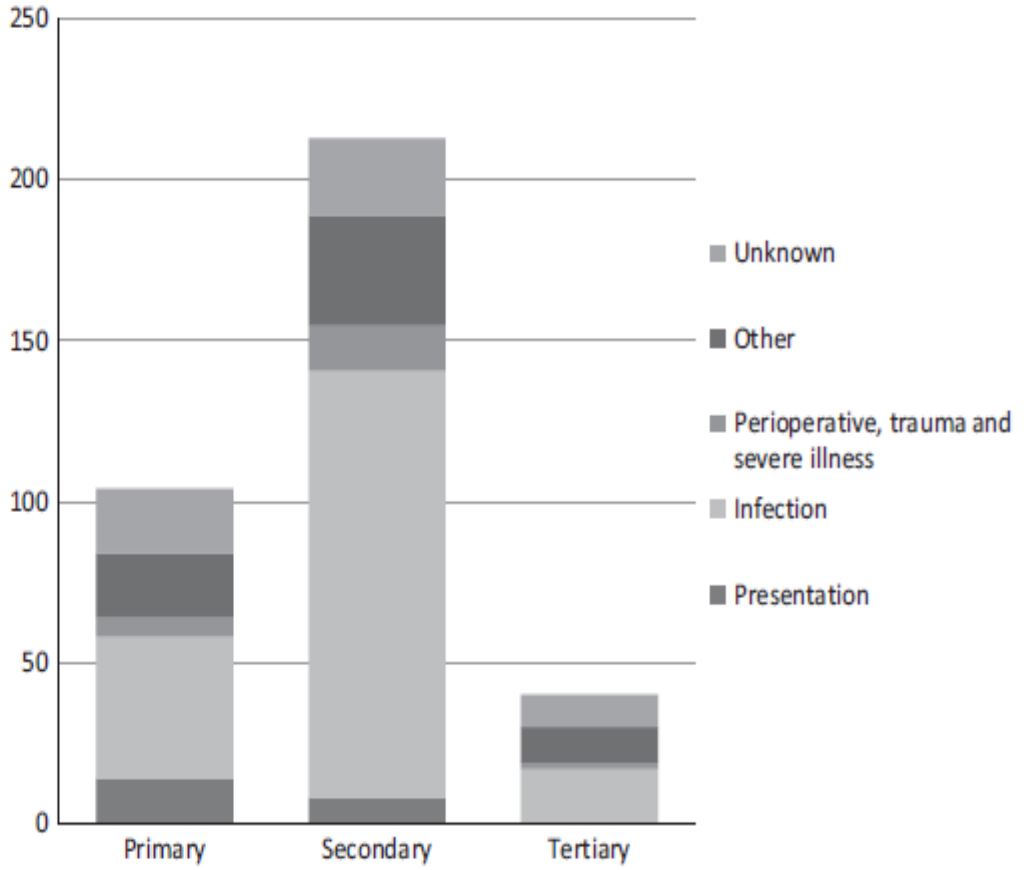


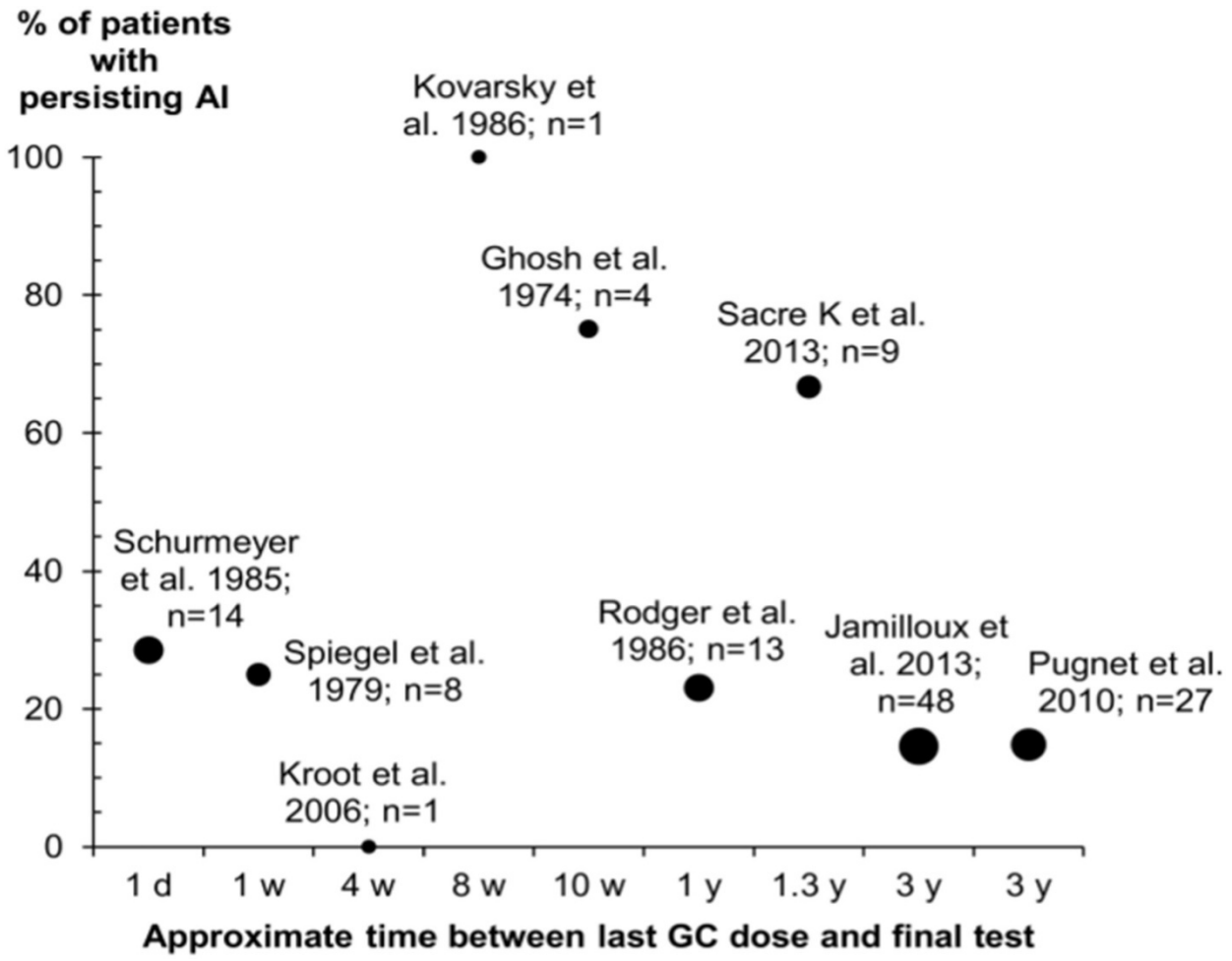
Fig. 1 Precipitating factors AI. Other, mental stress, physical stress, changes in GRT; Presentation, AC as presenting sign of AI.

AI and Drugs

Semin Arthritis Rheum. 2016 Mar 9. pii: S0049-0172(16)00091-3. doi: 10.1016/j.semarthrit.2016.03.001. [Epub ahead of print]

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

Joseph RM[1], Hunter AL[2], Ray DW[2], Dixon WG[3]



AI and HIV

JInt Assoc Provid AIDS Care. 2015 Jul-Aug; 14(4):300-5. doi:

Adrenal Insufficiency as a Result of Ritonavir and Exogenous Steroid Exposure: Report of 6 Cases and Recommendation for Management.

Wood BR[1], Lacy JM[2], Johnston C[3], Weigle DS[4], Dhanireddy S[3].

AI and HIV

Int J STD AIDS. 2001 Dec;12(12):804-10.

Prevalence of abnormal adrenocortical function in human immunodeficiency virus infection by low-dose cosyntropin test.

González-González JG[1], de la Garza-Hernández NE, Garza-Morán RA, Rivera-Morales IM, Montes-Villarreal J, Valenzuela-Rendón J, Villarreal-Pérez JZ

In conclusion, adrenocortical dysfunction occurs in approximately 20% of the cases with HIV disease. Clinical findings commonly occurring in HIV disease as well as adrenocortical insufficiency are not reliable indicators for performing adrenocortical laboratory assessment. Our results suggest screening all AIDS patients with the 10 microg cosyntropin test.

AI and antiphospholipid syndrome

Medicine (Baltimore). 2003 Mar;82(2):106-18.

Adrenal involvement in the antiphospholipid syndrome: clinical and immunologic characteristics of 86 patients.

Espinosa G[1], Santos E, Cervera R, Piette JC, de la Red G, Gil V, Font J, Couch R, Ingelmo M, Asherson RA

The results of the present review stress the clinical importance of systematic screening for lupus anticoagulant and anticardiolipin antibodies in all cases of adrenal hemorrhage or infarction. An initial screening for hypoadrenalism is mandatory in any antiphospholipid antibody-positive patient who complains of abdominal pain and undue weakness or asthenia In 31 (36%) patients, adrenal insufficiency was the first clinical manifestation of APS.

Patient (Ref.)	Clinical Manifestations of Adrenal Insufficiency	Adrenal CT/MRI Appearance
52 (34)	Abdominal pain, vomiting, fever, asthenia, hyperpigmentation, hypotension	Bilateral adrenal hemorrhage
53 (53)	Abdominal pain, hypotension, malaise	Bilateral adrenal hemorrhagic infarction
54 (38)	Fatigue, anorexia, nausea, vomiting, weight loss, hypotension	Bilateral enlargement adrenal glands
55 (65)	Left flank pain, nausea, diaphoresis	Unilateral adrenal hemorrhage
56 (19)	Left flank pain, fever, hypotension, confusion	Bilateral adrenal hemorrhage
57 (79)	Abdominal pain, weakness, fever, hypotension, asthenia, weight loss	Normal but bilateral adrenal hematomas 3 yr later
58 (5)	Abdominal pain, nausea, vomiting	Bilateral adrenal hemorrhagic infarction
59 (41)	Abdominal pain, hypotension	Bilateral adrenal infarction
60 (74)	Weakness, fatigue, anorexia, hypotension	Normal
61 (9)	Nausea, vomiting	Right adrenal mass interpreted as adrenal vein thrombosis/hemorrhagic infarction
62 (7)	Silent	ND
63 (31)	Abdominal pain, hypotension	ND
64 (36)	Silent	ND
65 (61)	Fever, thoracic pain	Bilateral adrenal hemorrhage
66 (73)	Ileus, weakness, hypotension, fever	Bilateral adrenal hemorrhage
67 (16)	Abdominal pain, fever, hypotension	ND
68 (26)	Abdominal pain, vomiting, diarrhea, lethargy, hypotension, fever	Bilateral adrenal necrosis
69 (42)	Abdominal pain, altered mental status,	Bilateral adrenal hemorrhage
70 (20)	Nausea, vomiting, hypotension	Left adrenal gland enlarged without evidence of hemorrhage or infarction
71 (67)	Silent	ND
72 (22)	Silent	ND
73 (90)	Silent	ND
74 (8)	Abdominal pain	ND
75 (8)	"Adrenal failure"	ND
76 (8)	Abdominal pain	Bilateral adrenal masses
77 (84)	Abdominal pain, fatigue, hypotension nausea, vomiting, hyperpigmentation	Bilateral hemorrhagic adrenal infarction
78 (89)	Diarrhea, hypotension, fever	Bilateral adrenal hemorrhage
79 (82)	Abdominal pain, fever, hypotension, confusion	Bilateral massive adrenal hemorrhage
80 (13)	Abdominal pain, vomiting, diarrhea, hypotension	Bilateral adrenal hemorrhage
81 (PS, Case 1)	Anorexia, weight loss, hypotension, vomiting	Bilateral adrenal glands enlarged with punctate calcifications
82 (PS)	Silent	Left large adrenal hemorrhagic mass
83 (PS)	Silent	Right adrenal hematoma
84 (PS)	Abdominal pain, diarrhea vomiting, fever	Bilateral adrenal hemorrhage
85 (PS)	Abdominal pain, hypotension fatigue, lethargy	Bilateral adrenal hemorrhage
86 (PS)	Silent	Right adrenal hemorrhage

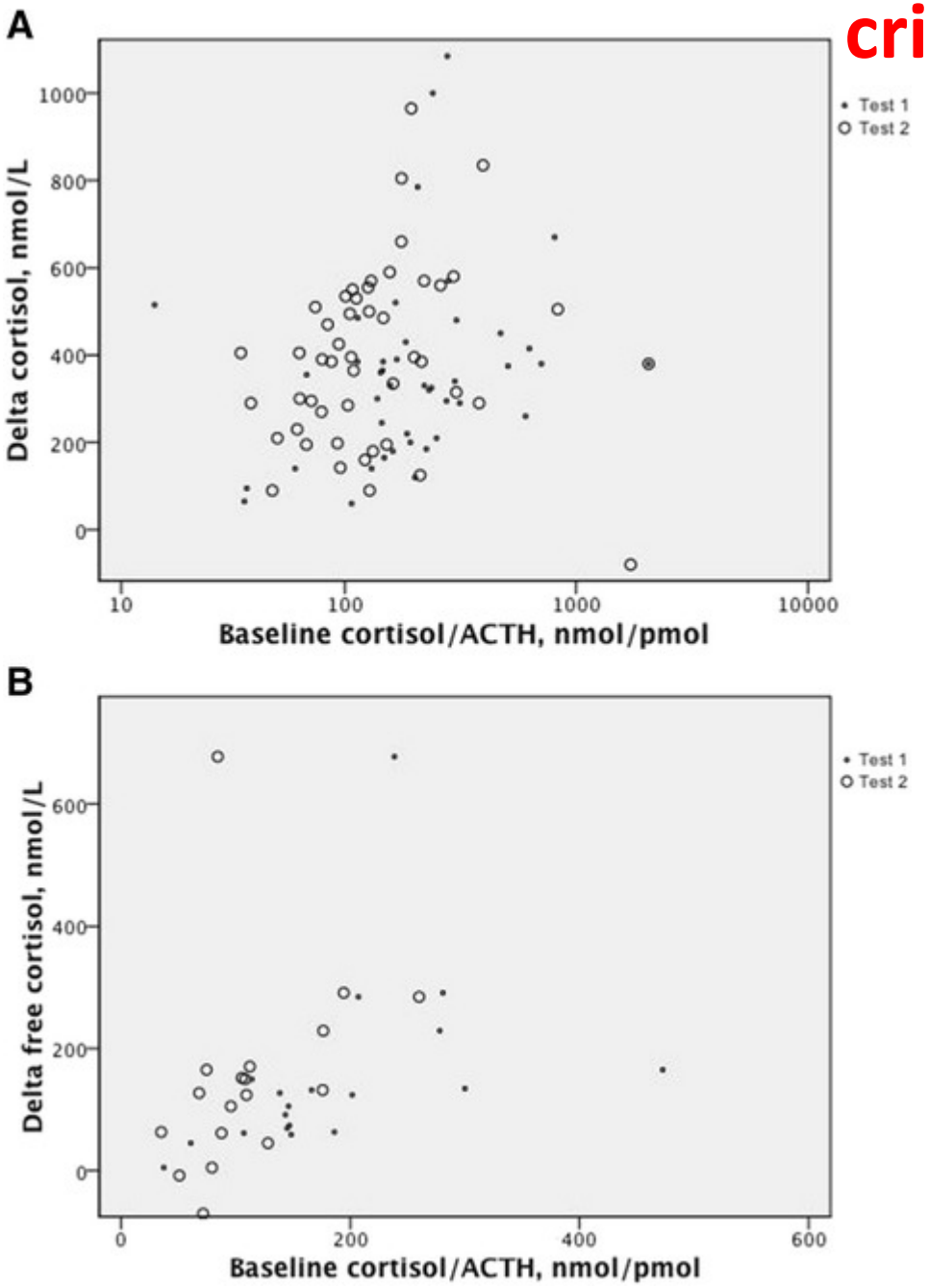
Abbreviations: ND = not done; CT/MRI = computed tomography/magnetic resonance imaging; PS = present series.

critical illness

Crit Care. 2015 Jan 6;19:1. doi: 10.1186/s13054-014-0721-8.

Diminished adrenal sensitivity to endogenous and exogenous adrenocorticotropic hormone in critical illness: a prospective cohort study.

de Jong MF et al.,



The cortisol-to-ACTH ratio at baseline and the subsequent response in increase in circulating total (A) and free (B) cortisol with exogenous ACTH: This suggests that ACTH-insensitive adrenals respond less with cortisol secretion to exogenous ACTH.

Differences between STC, SaC, cFC and CBG levels of the patients who have survived or not

critical illness

Days	Number	Survival	STC (μg/dL)		SaC (μg/dL)		cFC (μg/dL)		CBG (μg/dL)	
			Baseline	Peak	Baseline	Peak	Baseline	Peak	Baseline	Peak
D1	30	Alive	9.4 (3.1–25.8)	14.3 (7.4–46.9)	1.0 (0.2–7.5)	2.0 (0.6–15.0)	0.3 (0.1–0.9)	0.5 (0.3–1.7)	0.3 (0.1–0.6)	0.4 (0.2–0.5)
		Dead	21.0 (4.6–53.2)	31.0 (7.5–52.0)	2.3 (0.2–9.0)	3.4 (0.5–17.8)	0.8 (0.2–1.87)	1.1 (0.3–1.9)	0.2 (0.1–0.5)	0.3 (0.1–0.5)
D2	22	Alive	12.4 (4.9–40.9)		0.7 (0.1–3.3)		0.4 (0.2–1.4)		0.2 (0.1–0.5)	
		Dead	17.7 (5.6–24.8)		0.6 (0.1–5.2)		0.8 (0.3–1.5)		0.2 (0.2–0.5)	
D3	20	Alive	10.2 (3.2–31.3)		0.7 (0.1–3.8)		0.3 (0.1–1.1)		0.2 (0.1–0.5)	
		Dead	22.8 (7.9–43.3)		0.9 (0.1–5.2)		0.8 (0.3–1.5)		0.2 (0.2–0.4)	
D4	20	Alive	12.6 (3.5–22.1)		0.8 (0.1–3.0)		0.5 (0.1–0.8)		0.3 (0.1–0.4)	
		Dead	18.6 (3.3–50.5)		2.2 (0.2–9.4)		0.7 (0.1–1.8)		0.3 (0.1–0.4)	
D5	19	Alive	11.4 (5.2–30.4)		0.8 (0.1–4.6)		0.4 (0.2–1.1)		0.3 (0.1–0.4)	
		Dead	20.2 (15.6–30.0)		0.7 (0.1–3.1)		0.7 (0.6–1.1)		0.2 (0.2–0.4)	
D6	17	Alive	10.4 (2.1–43.0)		1.0 (0.1–4.6)		0.4 (0.1–1.5)		0.2 (0.1–0.5)	
		Dead	27.3 (5.6–32.6)		2.0 (0.9–4)		1.0 (0.2–1.2)		0.3 (0.1–0.4)	
D7	14	Alive	6.9 (0.4–13.9)	9.9 (3.9–25.0)	0.5 (0.3–3.0)	1.7 (0.2–4.0)	0.2 (0.1–0.5)	0.4 (0.1–0.9)	0.3 (0.2–0.5)	0.4 (0.2–0.5)
		Dead	8.7 (5.6–12.4)	13.3 (8.3–18.8)	0.9 (0.6–4.6)	2.4 (0.6–2.9)	0.3 (0.2–0.4)	0.5 (0.3–0.7)	0.3 (0.2–0.5)	0.3 (0.1–0.4)
*p*1			*0.02*	0.53	0.28	0.12	*0.02*	*0.01*	0.39	0.27
*p*2			0.08		0.64		0.57		0.56	
*p*3			0.55		0.69		0.06		0.36	
*p*4			*0.02*		0.32		0.55		0.91	
*p*5			*0.02*		0.9		*0.02*		0.44	
*p*6			0.3		0.2		0.3		0.5	
*p*7			*0.01*	0.24	0.07	0.39	*0.01*	0.24	0.94	0.35

Care. 2016; 4: 3 **Comparison of total, salivary and calculated free c**J Intensive **ortisol levels in patients with severe sepsis** Gulsah Elbuken et al.

Lower STC levels is not associated with increased mortality in patients with SS.

Insufficienza surrenalica

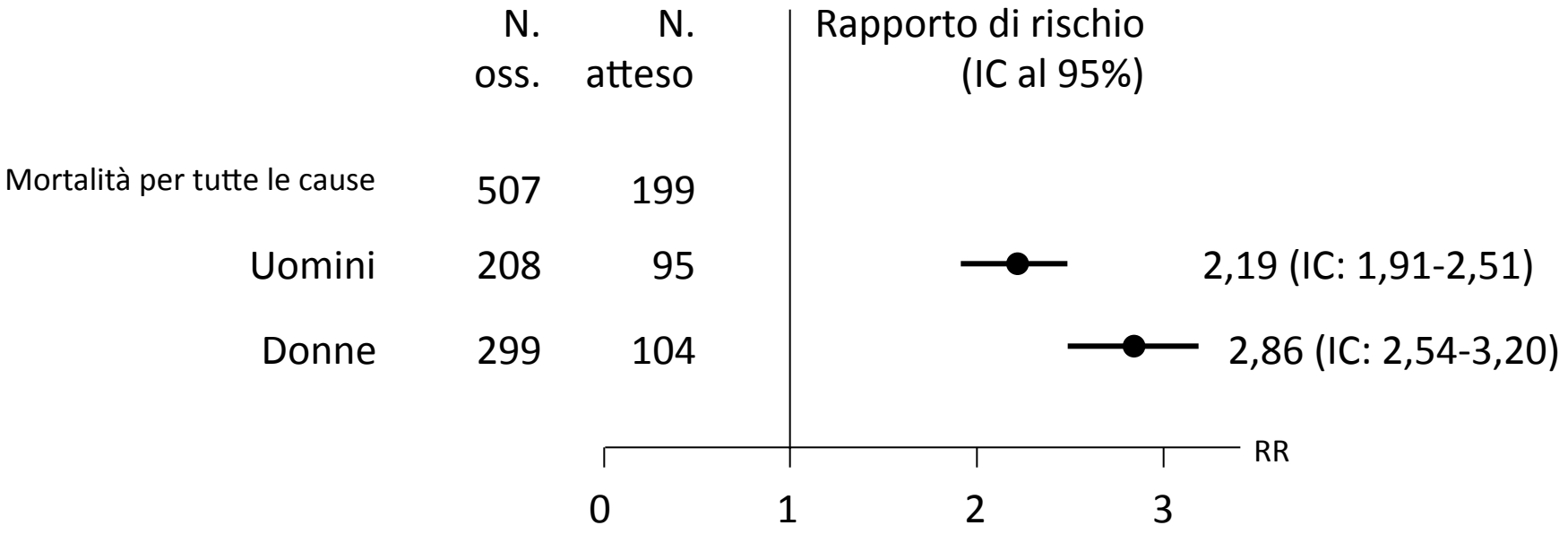
Malattia potenzialmente fatale

- **La maggior parte dei pazienti non trattati è deceduta nei 2 anni successivi alla diagnosi in assenza di terapia sostitutiva[1]**

1. Dunlop D. *Br Med J* 1963;2: 887-891

Tasso di mortalità nell'IS trattata

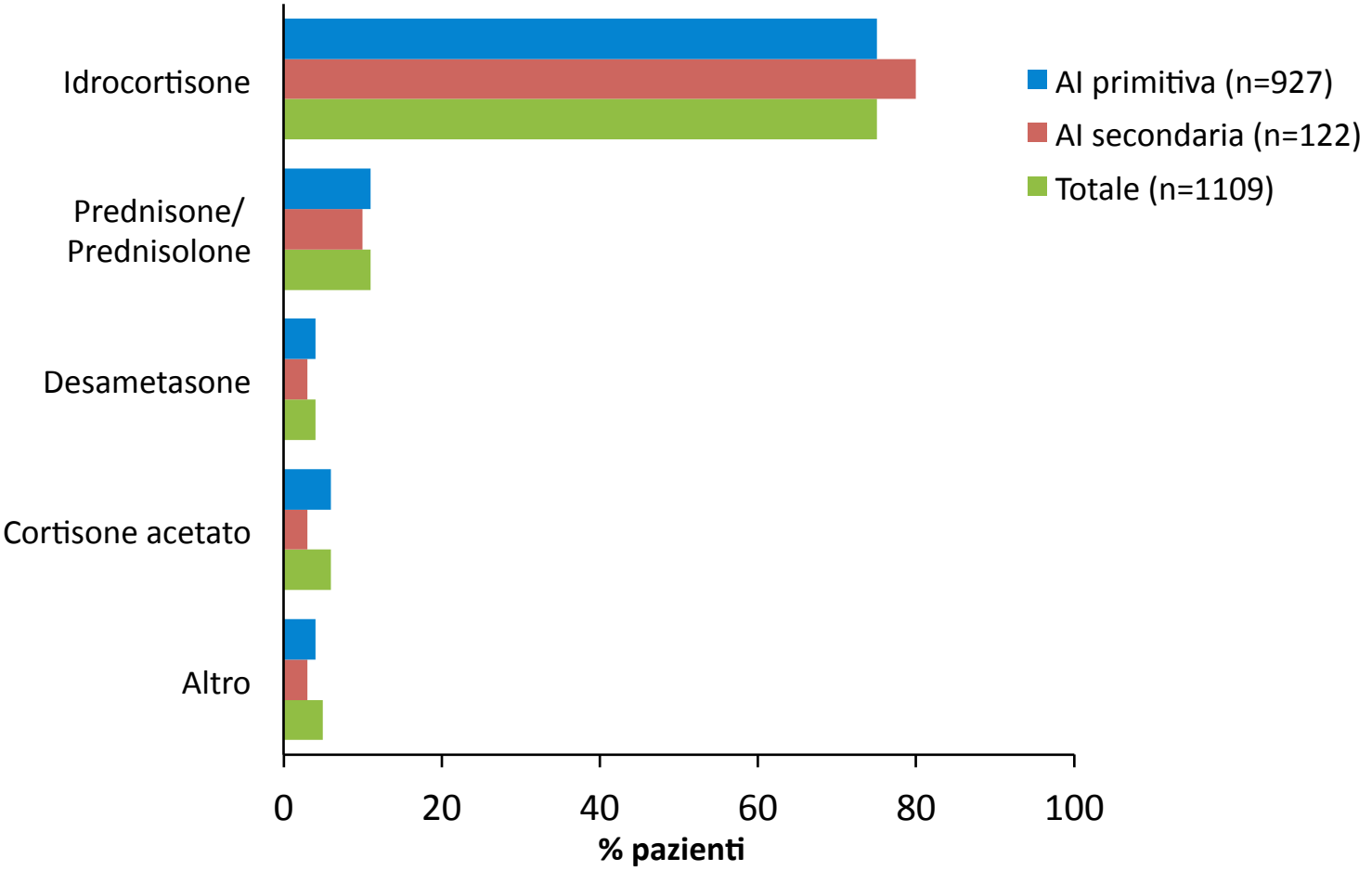
1675 pazienti svedesi identificati nei Registri nazionali svedesi degli ospedali e delle cause di morte 1987 - 2001[1]



1. Bergthorsdottir R et al. J Clin Endocrinol Metab 2006;91:4849-53

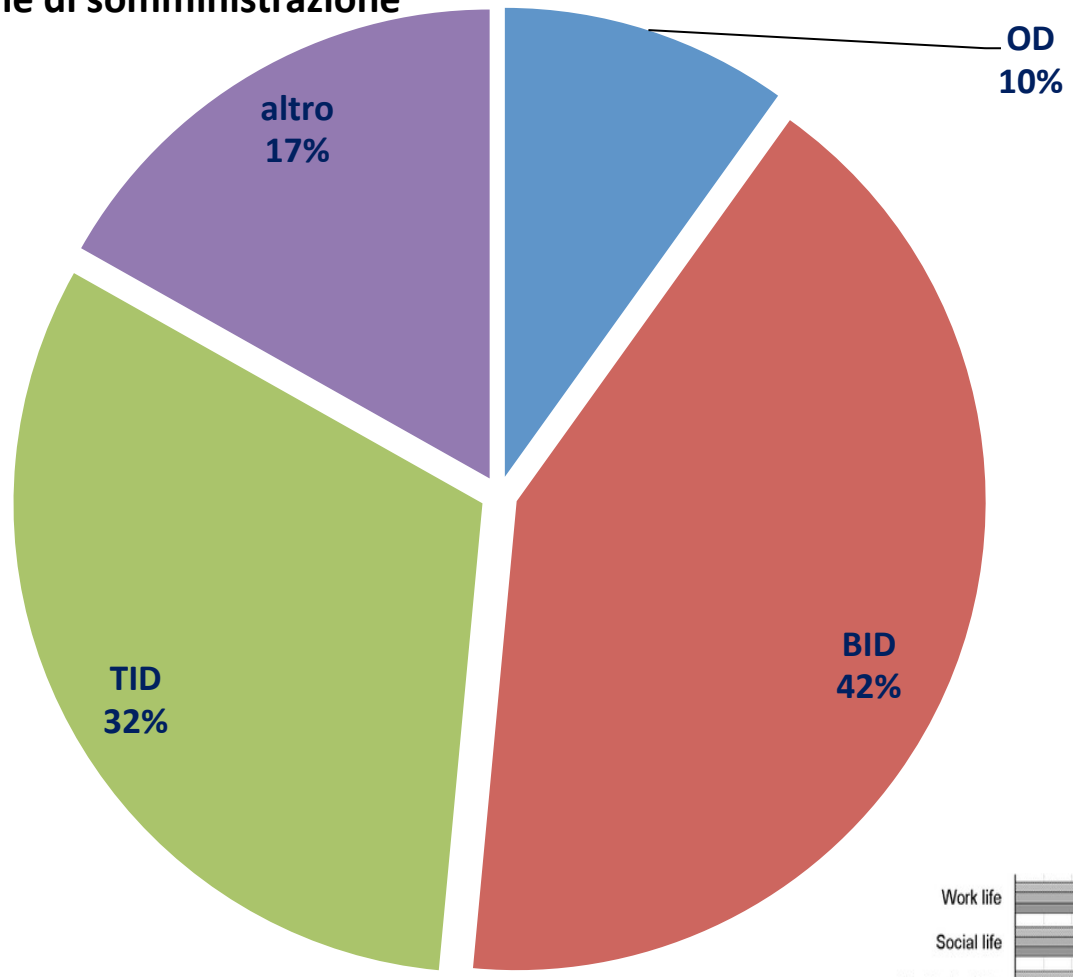
Terapia sostitutiva glucocorticoide dell'insufficienza surrenalica: trattamenti in uso[1]

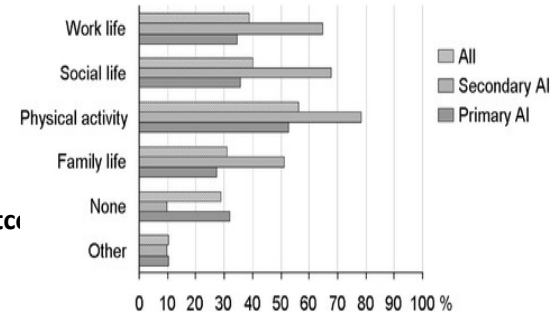
Risultati di un'indagine tramite questionario condotta nel 2008 su 1245 pazienti con AI primitiva (84%) o secondaria (11%) provenienti da 34 Paesi (~20% degli intervistati provenivano dall'Europa; ~60% dagli Stati Uniti)



1. Forss M et al. BMC Endocr Disord 2012;12:8

Regime di somministrazione





BMC Endocr Disord. 2012 Jun 13;12:8. doi: 10.1186/1472-6823-12-8.

Current practice of glucocorticoid replacement therapy and patient-perceived health outc insufficiency - a worldwide patient survey.

Forss M[1], Batcheller G, Skrtic S, Johannsson G

Cortone Acetato

- Compared with HC, it shows a lower serum cortisol peak and delayed clearances of cortisol (2 daily doses; possible advantage)

- Cortisone acetate requires activation to cortisol by hepatic 11betaHSD1, which contributes to a higher pharmacokinetic variability compared to HC. This conversion could be impaired in:
  - Patients with congenital Cortisone Reductase Deficiency
  - Patients treated with rhGH (GH may inhibit 11betaHSD1 expression)
  - patients with advanced liver disease.

Idrocortisone

- Hydrocortisone, i.e cortisol, do not require hepatic activation.
- HC shows a higher serum cortisol peak, followed by a rapid decline (< 3 ug/dl 5- 7 h after ingestion).

- Patient compliance with thrice-daily dosing is far from absolute for many patients; possible increased risk of adrenal crisis, especially for older patients

Trattamenti in uso, dosi equivalenti

Farmaco	Dose di idrocortisone equivalente	Effetto mineralcorticoide	Effetto antinfiammatorio	Durata dell'effetto[1]
Idrocortisone	20 mg	Sì	1	Breve
Cortisone acetato	25 mg	Sì	0,8	Breve
Prednisolone	5 mg	Sì	3	Intermedia
Desametasone	0,75 mg	No	25	Lunga

[1] Emivita biologica: breve = 8-12 ore, intermedia = 12-36 ore, lunga = 36-72 ore

Olsson T, Valdemarsson S. Läkemedelsboken 2011-2012, p. 641-54.

Ritmo circadiano del cortisolo nei volontari sani

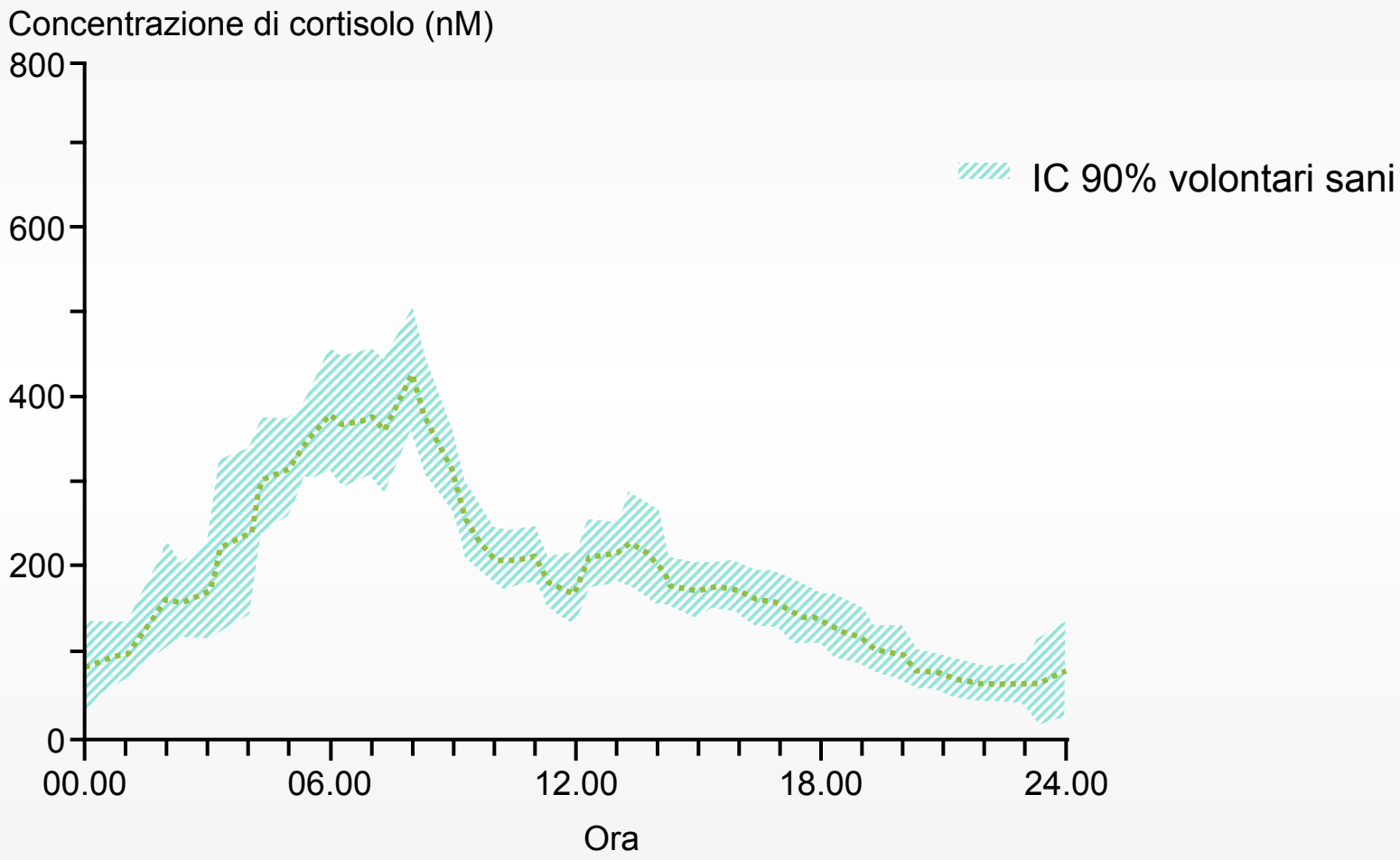
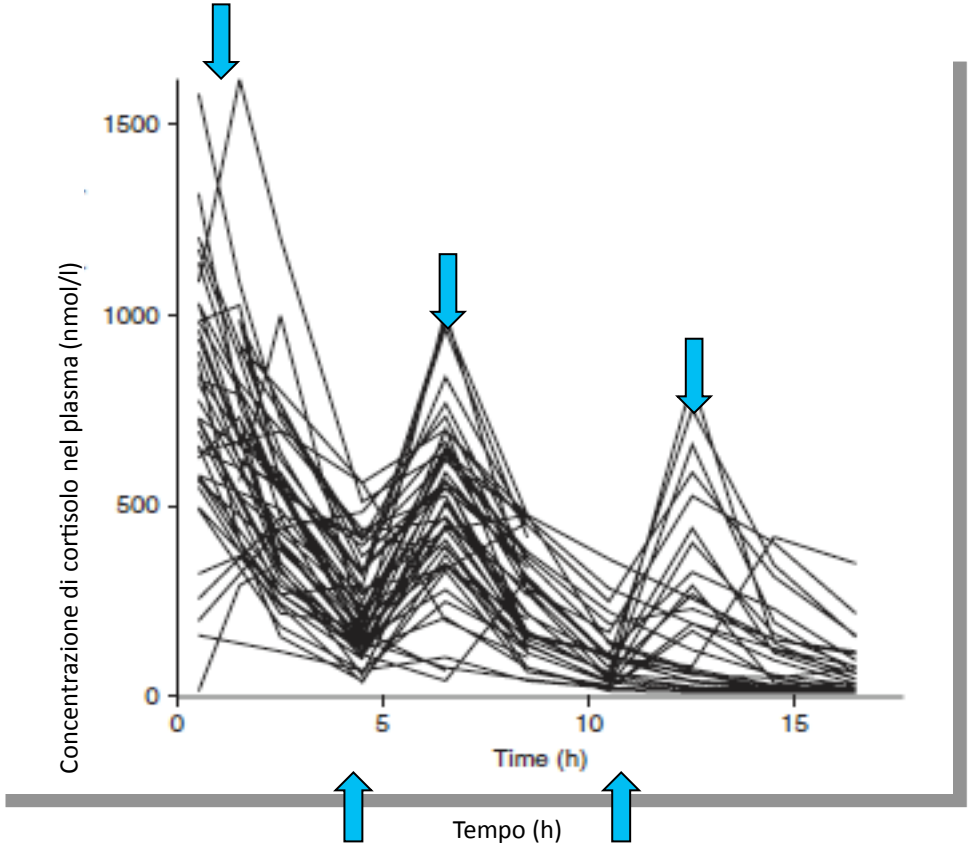


Figura adattata da Vgontzas AN et al. J Clin Endocrinol Metab 2001;86:3787–3794

Profili di farmacocinetica dei pazienti con IS trattati con idrocortisone a rilascio immediato[1]



7.30 **17.30** **22.30**

Tratto da ref. 1

Insufficienza surrenalica (n)	
Primaria	20
Secondaria	30
Dosi/die (n)	
1	4
2	24
3	22

Dose media: 25 mg/die (DS: 6)

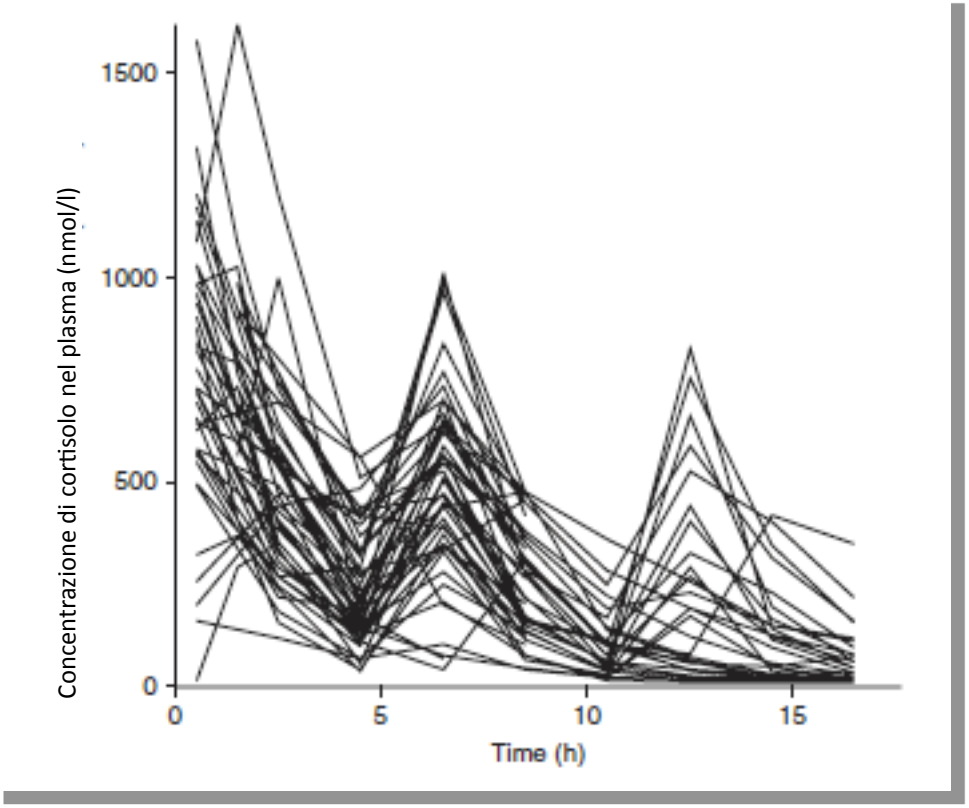
Intervallo: 15–50 mg/die

Circa 13 diversi regimi posologici utilizzati

Observed values were compared with the endogenous physiological cortisol throughout the day (0800, 1600 and 0000 h). The regimen with the highest proportion of simulated patients within the physiological targets was 10 + 5 + 5 mg at 0730, 1200 and 1630 h, respectively. However, even with this regimen, about 54%, 44% and 32% of patients would remain over- or under-treated at 0800, 1600 and 2400 h, respectively.

1. Simon N, et al. Clin Pharmacokinet 2010; 49; 455-63

Gli elevati livelli di cortisolo serali sono stati associati ad alcune co-morbilità



I livelli serali elevati sono associati a:[2-6]

- Intolleranza al glucosio[2]
- Obesità addominale[3]
- Calcificazione coronarica[4]
- Insonnia e ridotta qualità del sonno[5,6]

1. Johannsson G, et al. *J Clin Endocrinol Metab.* 2012;97:473-81. **2.** Plat L, et al. *J Clin Endocrinol Metab*. 1999;84: 3082-92. **3.** Gangwisch JE, *Obes Rev.* 2009;10 Suppl 2: 37-45. **4.** Matthews K, et al. *Psychos Med.* 2006;68: 657-61 **5.** Garcia-Borreguero D, et al. *J Clin Endocrinol Metab*. 2000;85: 4201-6. **6.** Vgontzas AN, et al. *J Clin Endocrinol Metab*. 2001;86: 3787-94 **.**

Nonostante il trattamento attuale, gli esiti per i pazienti con IS restano insoddisfacenti[1-6]

Terapia sostitutiva convenzionale con glucocorticoidi

- Mortalità prematura[1]
- Elevata frequenza di ricoveri ospedalieri/ infezioni[2]
- Compromissione del benessere e della QoL[3]
- Profilo metabolico compromesso[4]
- Riduzione della densità minerale ossea[5,6]

1. Bergthorsdottir R, et al. *JCEM* 2006;91:4849–53.
2. *Smans LCCJ, et al. European Journal of Endocrinology 2013; 168: 609-614*
3. *Hahner S, et al. JCEM 2007;92:3912–22.*
4. *Filipsson H, et al. JCEM 2006;91:3954–61*.
5. Zelissen PM, et al. *Ann Intern Med 1994*;120:207–10.
6. Løvås K, et al. *EJE* 2009;160:993–1002**.**

European Journal of Endocrinology (2008) 159 811–817 ISSN 0804-4643

CLINICAL STUDY

Impaired subjective health status in chronic adrenal insufficiency: impact of different glucocorticoid replacement regimens

Benjamin Bleicken*, Stefanie Hahner[1,*], Melanie Loeffler[1], Manfred Ventz, Bruno Allolio[1] and Marcus Quinkler

Clinical Endocrinology (2010) 72, 297–304 doi: 10.1111/j.1365-2265.2009.03596.x

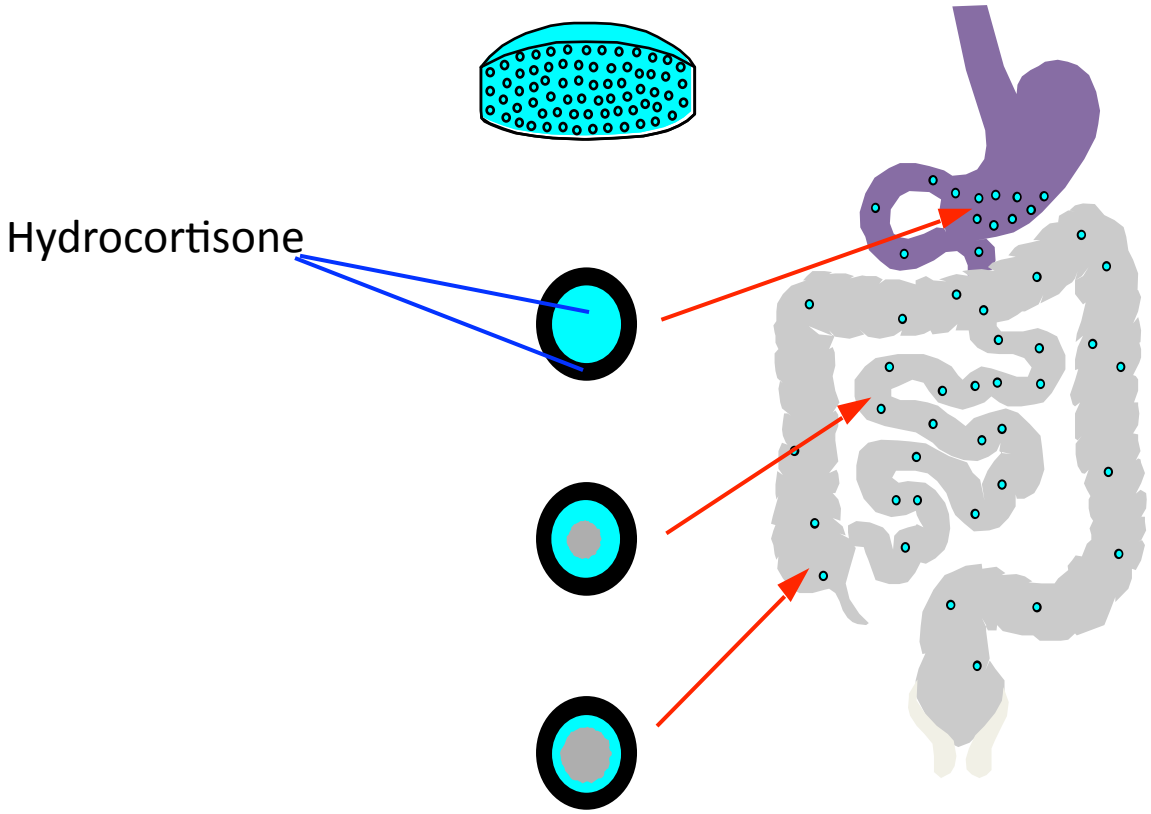
ORIGINAL ARTICLE

Influence of hydrocortisone dosage scheme on health-related quality of life in patients with adrenal insufficiency

Benjamin Bleicken*,**, Stefanie Hahner†,**, Melanie Loeffler†, Manfred Ventz*, Oliver Decker†, Bruno Allolio† and Marcus Quinkler*

Health-related QoL was impaired in patients with primary and secondary AI. HC doses above 30 mg/day were associated with a worse health status. Thrice daily intake of HC was not superior to twice daily intake.
Our data support the perception that current replacement strategies are still insufficient to fully restore well-being and daily performance.

Delivering physiological cortisol
combination of immediate and controlled release

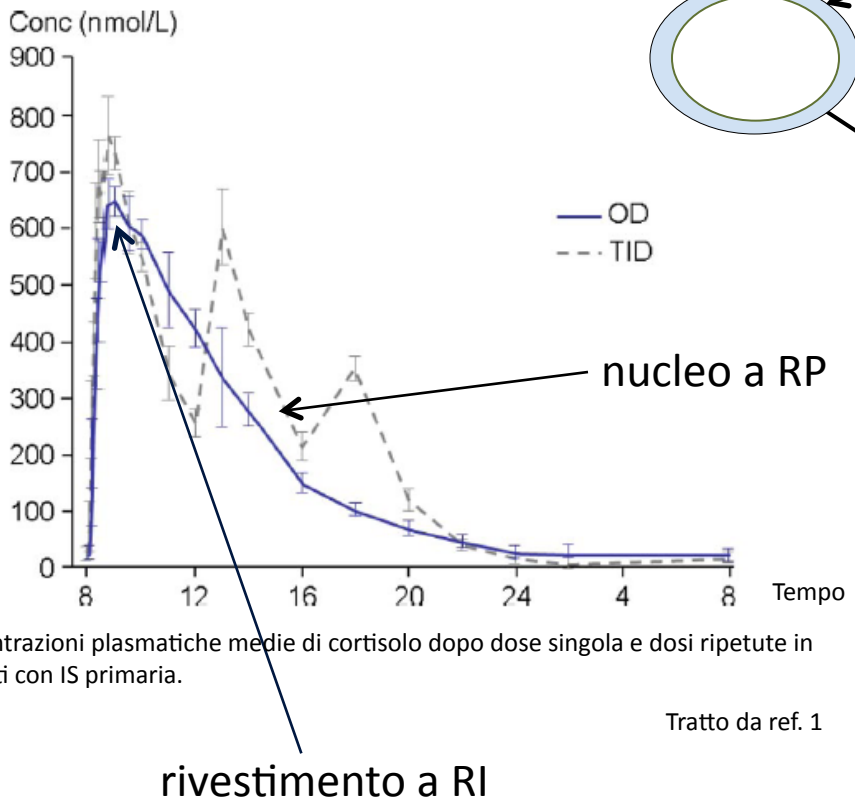


- The small intestine is the site for the most rapid absorption of orally administered drug[1].
- It is expected that drug absorption in the mid- to distal colon will demonstrate high intra- and interindividual variability[1]

[1] Lennernäs *et al*. Expert Opin Drug Metab Toxicol 2008; 4(6)

Idrocortisone a rilascio modificato

La duplice azione simula meglio il profilo fisiologico di rilascio del cortisolo rispetto alle terapie attuali con glucocorticoidi[1]



Concentrazioni plasmatiche medie di cortisolo dopo dose singola e dosi ripetute in pazienti con IS primaria.

Tratto da ref. 1

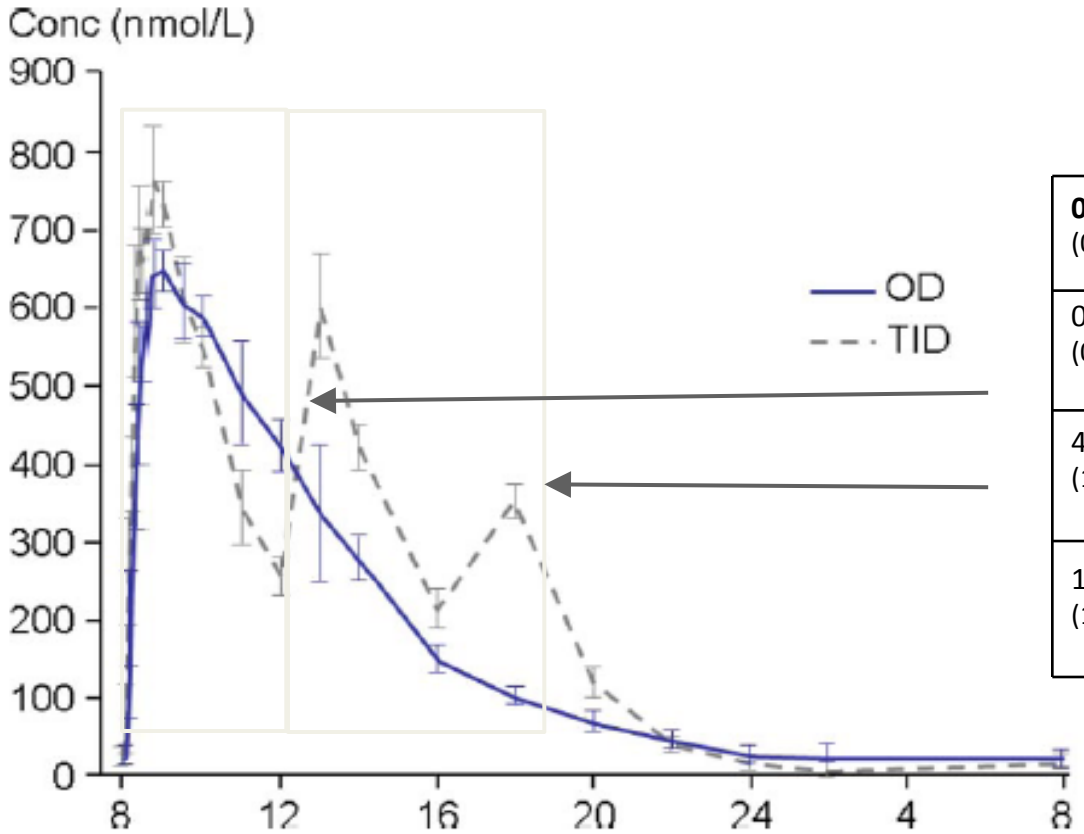
- Il **rivestimento a rilascio immediato (RI)** fornisce concentrazioni fisiologiche mattutine di cortisolo entro 20 minuti dall'assunzione[1]
- Il **nucleo a rilascio prolungato (RP)** fornisce un profilo di cortisolo sierico costante nell'arco della giornata[1]

OD = Plenadren una volta al giorno

TID = idrocortisone a rilascio immediato tre volte al giorno

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

Miglioramento del profilo del cortisolo sierico con idrocortisone a rilascio modificato vs. TID[1]



0-24 h (08.00-08.00)	**Esposizione totale del 19,4% inferiore con PLENADREN rispetto a TID**
0-4 h (08.00-12.00)	Esposizione mattutina del 6,4% più **elevata** con PLENADREN rispetto a TID
4-10 h (12.00-18.00)	Esposizione nel pomeriggio e prima serata del 30,5% **inferiore** con PLENADREN rispetto a TID
10-24 h (18.00-08.00)	Esposizione notturna del 58,8% **inferiore** con PLENADREN rispetto a TID

OD = Plenadren una volta al giorno

TID = idrocortisone a rilascio immediato tre volte al giorno

Concentrazioni plasmatiche medie di cortisolo dopo dose singola e dosi ripetute in pazienti con IS primaria.

Tratto da ref. 1

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

Panoramica degli studi clinici

Fase	Studio (obiettivi)	Disegno dello studio	N. di pazienti
I	**Johannsson et al. 2009**[1] (FC, tollerabilità, interazione con il cibo)[1]	Monocentrico, in doppio cieco, randomizzato, controllato, crossover con trattamento con idrocortisone a rilascio modificato 5 e 20 mg	16 volontari sani
II/III	**Johannsson et al. 2012**[2] (FC, efficacia, tollerabilità e sicurezza, qualità della vita (QoL))	**Parte A:** Studio controllato multicentrico, in aperto, randomizzato, a due bracci, crossover a due periodi, di idrocortisone orale a rilascio modificato (una volta al giorno [OD]; PLENADREN) e idrocortisone orale convenzionale (tre volte al giorno [TID]**)** **Parte B:** Periodo di estensione in aperto di 6 mesi con PLENADREN	64 pazienti con insufficienza surrenalica primaria
IIIb	**Nilsson et al. 2014**[3] (sicurezza, tollerabilità, efficacia, QoL)	Studio multicentrico in aperto di idrocortisone a rilascio modificato per via orale (PLENADREN OD) (estensione dello studio di fase II/III)	71 pazienti con insufficienza surrenalica primaria

1. Johannsson G et al. Eur J Endocrinol 2009;161:119–30;
2. Johannsson G et al. J Clin Endocrinol Metab 2012;97:473-81;

Variabili metaboliche osservate con idrocortisone a rilascio modificato vs. terapia TID[1]

Differenza PLENADREN – TID in tutti i pazienti dopo 12 settimane[1]

	(media ± DS)	
Peso corporeo*	-0,7 kg	p=0,005 n=64
SBP	-5,5 mm Hg	p=0,0001 n=64
DBP	-2,3 mm Hg	p=0,03 n=64
$HbA1_c$	-0,1 ± 0,4 %	p=0,0006 n=57

DBP = pressione arteriosa diastolica
TID = idrocortisone a rilascio immediato tre volte al giorno
SBP = pressione arteriosa sistolica

*Esiste una tendenza generale al calo ponderale. Va notato che l'RCP include aumento ponderale tra gli effetti indesiderati dopo somministrazione di Plenadren.[2]

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

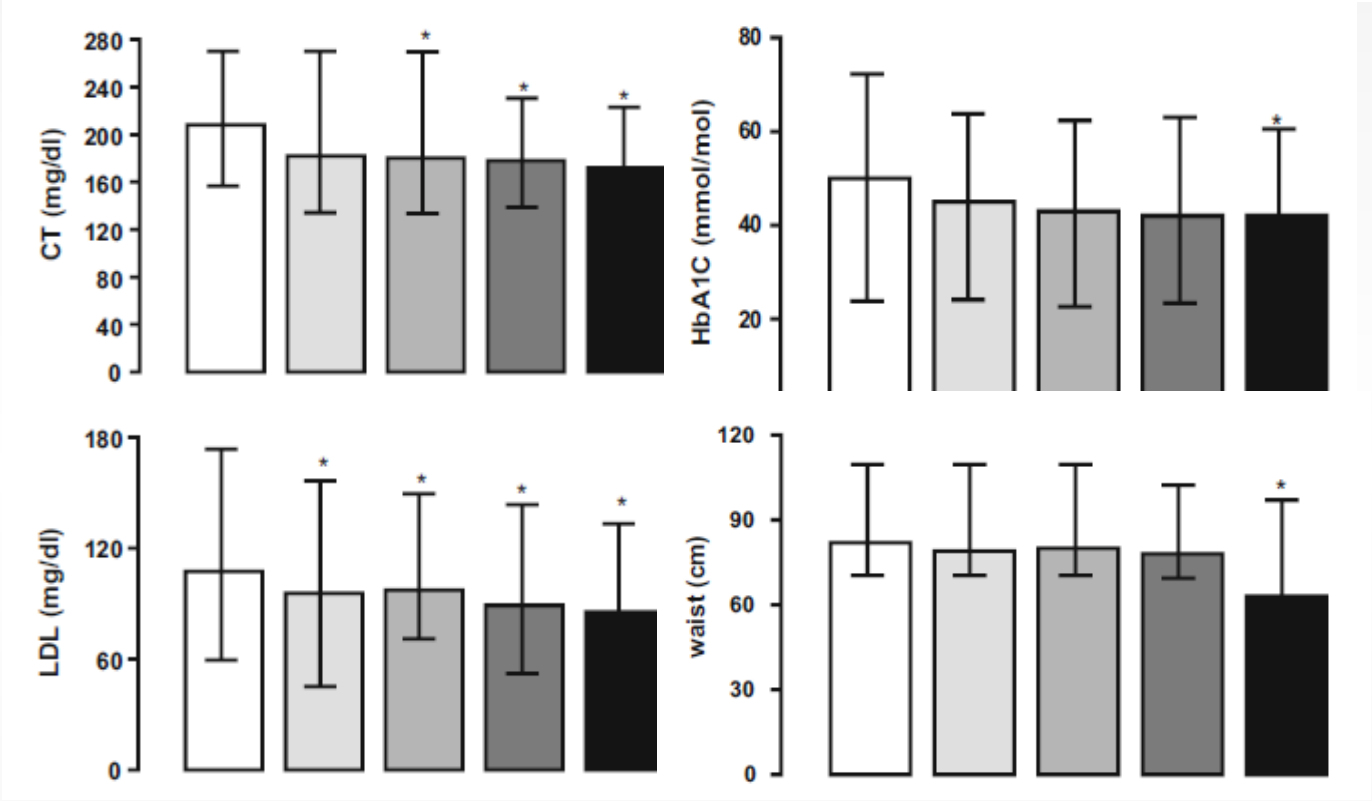
PLENADREN può essere usato durante la gravidanza.
Non vi sono indicazioni che la terapia sostitutiva con idrocortisone sia associata a esiti avversi per la madre e/o il feto.

PLENADREN può essere usato durante l'allattamento al seno.

- **Switch da idrocortisone orale 3 vv/die → dosaggio equivalente di Plenadren e personalizzazione della dose.**
- **Uso nelle malattie intercorrenti:**
  - **Casi gravi** (gravi infezioni, gastroenterite con vomito/diarrea, febbre alta, stress fisico intenso, gravi incidenti, intervento chirurgico in anestesia generale) aumento immediato della dose e sostituzione con **trattamento parenterale**.
  - **Casi meno gravi**: dose orale aumentata temporaneamente con 2 o 3 somministrazioni al giorno con intervalli di 8 ± 2 ore (aumento delle somministrazioni e non della dose del mattino). Si può aggiungere idrocortisone a rilascio immediato a Plenadren.

Improvement of anthropometric and metabolic parameters, and quality of life following treatment with dual-release hydrocortisone in patients with Addison's disease

Roberta Giordano[1,2] · Federica Guaraldi[2] · Elisa Marinazzo[2] · Federica Fumarola[2] · Alessia Rampino[1] · Rita Berardelli[4] · Ioannis Karamouzis[2] · Manuela Lucchiari[3] · Tilde Manetta[3] · Giulio Mengozzi[3] · Emanuela Arvat[4] · Ezio Ghigo[2]



Miglioramento complessivo del profilo lipidico, girovita ed emoglobina glicosilata al termine del trattamento con Idrocortisone RM

In conclusione lo studio fornisce ulteriori evidenze in merito al miglioramento di parametri metabolici, antropometrici e QoL in pazienti affetti da IS primaria trattati con PLENADREN

Giordano R. et al. Endocrine 2015 Jul 17. [Epub ahead of print]

Modified-release hydrocortisone decreases BMI and HbA1c in patients with primary and secondary adrenal insufficiency

Marcus Quinkler[1,2], Roy Miodini Nilsen[3], Kathrin Zopf[2], Manfred Ventz[2] and Marianne Øksnes[4,5]

Correspondence

Andamento nel corso del follow-up dei parametri metabolici monitorati nei pazienti in trattamento con Idrocortisone RM ed Idrocortisone RI

Table 3 AddiQoL scores and metabolic parameters in patients with adrenal insufficiency ($n = 50$) at baseline and follow-up after receiving modified release hydrocortisone or conventional hydrocortisone.

	Baseline		Follow-up		Estimated change per 30 days[a]			
Outcome	No. of patients	Observed mean ± S.E.M.	No. of patients	Observed mean ± S.E.M.	$\beta \pm$ S.E.M.	*P* change	Adjusted $\beta \pm$ S.E.M.[b]	Adjusted P change
AddiQoL								
Modified release HC	30	83.8 ± 1.81	30	84.9 ± 1.95	0.157 ± 0.167	0.348	0.081 ± 0.167	0.629
Conventional HC	20	84.0 ± 2.11	20	80.9 ± 2.50	−0.299 ± 0.130	0.021	−0.305 ± 0.127	0.016
interaction[c]					0.031		0.066	
Fatigue								
Modified release HC	30	22.4 ± 0.68	30	22.6 ± 0.81	0.047 ± 0.064	0.464	0.017 ± 0.064	0.793
Conventional HC	20	21.1 ± 0.66	20	19.9 ± 0.85	−0.108 ± 0.050	0.030	−0.110 ± 0.049	0.024
interaction[c]					0.057		0.116	
BMI							−0.056 ± 0.020[d]	
Modified release HC	30	26.0 ± 0.75	30	25.6 ± 0.71	−0.057 ± 0.019	0.003	0.000 ± 0.015[d]	0.006
Conventional HC	20	25.7 ± 1.14	20	25.8 ± 1.08	0.002 ± 0.015	0.887	0.029[d]	0.985
interaction[c]					0.015			
HbA1c							−0.023 ± 0.008[e]	
Modified release HC	27	6.04 ± 0.29	28	5.86 ± 0.28	−0.020 ± 0.008	0.014	0.001 ± 0.006[e]	0.005
Conventional HC	20	5.63 ± 0.13	18	5.72 ± 0.15	−0.0002 ± 0.006	0.975	0.017e	0.807
interaction[c]					0.049		0.017e	
Cholesterol								
Modified release HC	30	213.8 ± 7.97	29	200.1 ± 7.57	−1.835 ± 0.760	0.016	−1.655 ± 0.787	0.036
Conventional HC	19	221.8 ± 10.8	19	210.9 ± 13.1	−0.586 ± 0.604	0.332	−0.605 ± 0.608	0.320
Interaction[c]					0.198		0.294	
HDL								
Modified release HC	30	65.4 ± 3.5	29	62.7 ± 3.3	−0.302 ± 0.231	0.190	−0.317 ± 0.240	0.188
Conventional HC	19	62.5 ± 4.3	19	61.2 ± 5.0	−0.187 ± 0.183	0.306	−0.177 ± 0.186	0.340
interaction[c]					0.696		0.647	
LDL								
Modified release HC	30	127.2 ± 7.6	29	121.4 ± 7.0	−0.912 ± 0.485	0.060	−0.716 ± 0.496	0.149
Conventional HC	19	133.9 ± 9.1	18	128.4 ± 11.1	0.037 ± 0.388	0.925	0.010 ± 0.385	0.980
interaction[c]					0.127		0.251	
Triglycerides								
Modified release HC	30	115.7 ± 11.9	29	120.9 ± 11.3	0.944 ± 1.828	0.605	1.571 ± 1.889	0.406
Conventional HC	19	149.3 ± 16.4	19	173.4 ± 26.7	0.333 ± 1.462	0.820	0.376 ± 1.471	0.798
interaction[c]					0.794		0.619	

Tendenza al miglioramento degli indici di qualità della vita (QoL) a 12 settimane[1]

- Variazioni costanti in termini di QoL a favore di PLENADREN a 12 settimane nel questionario FIS (Fatigue Impact Scale) vs. TID[1]:
  - Funzionalità psicosociale (p=0,04)
  - Funzionalità cognitiva (p=0,054)
  - Punteggio totale (p=0,08)

- Nel questionario Psychological General Well-Being, il punteggio totale è risultato a favore di PLENADREN vs. TID a 12 settimane (p=0,06)[1]

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

AddiQoL

Qualità della vita correlata alla salute nella malattia di Addison

Il questionario serve a valutare cosa ne pensa della sua salute nelle ultime quattro settimane e come giudica in generale la qualità della sua vita. Risponda a tutte le domande e non rifletta troppo nel rispondere, poiché una risposta veloce è probabilmente più veritiera.

	Mai	Quasi mai	Qualche volta	Il più delle volte	Quasi sempre	Sempre
Mi sento bene						
Posso andare avanti tutto il giorno senza stancarmi						
Le normali attività giornaliere mi stancano						
Mi devo sforzare per completare il mio lavoro						
Mi devo forzare per fare le cose						
Perdo il filo del discorso						
Dormo bene						
Quando mi sveglio al mattino mi sento riposato						
Appena sveglio al mattino mi sento poco bene						
Sono soddisfatto della mia vita sessuale						
Mi sento rilassato						
Mi sento giù o depresso						
Mi sento nervoso o irritabile						
Ho difficoltà a pensare con chiarezza						
Mi sento stordito o confuso						
Sudo senza apparente motivo						

	Mai	Quasi mai	Qualche volta	Il più delle volte	Quasi sempre	Sempre
Ho mal di testa						
Ho la nausea						
Ho dolori muscolari e/o articolari						
Ho mal di schiena						
Mi sento le gambe deboli						
Mi preoccupo per la mia salute						
La mia capacità di lavoro è limitata						
Riesco a concentrarmi facilmente						
Sono felice						
Mi sento pieno di energia						

	Assolu-tamente falso	Falso	In parte falso	In parte vero	Vero	Assolu-tamente vero
Mi sento fisicamente in forma						
Mi ammalo più facilmente degli altri						
Impiego molto a guarire dalle malattie						
Reggo bene le emozioni						

Uso prolungato

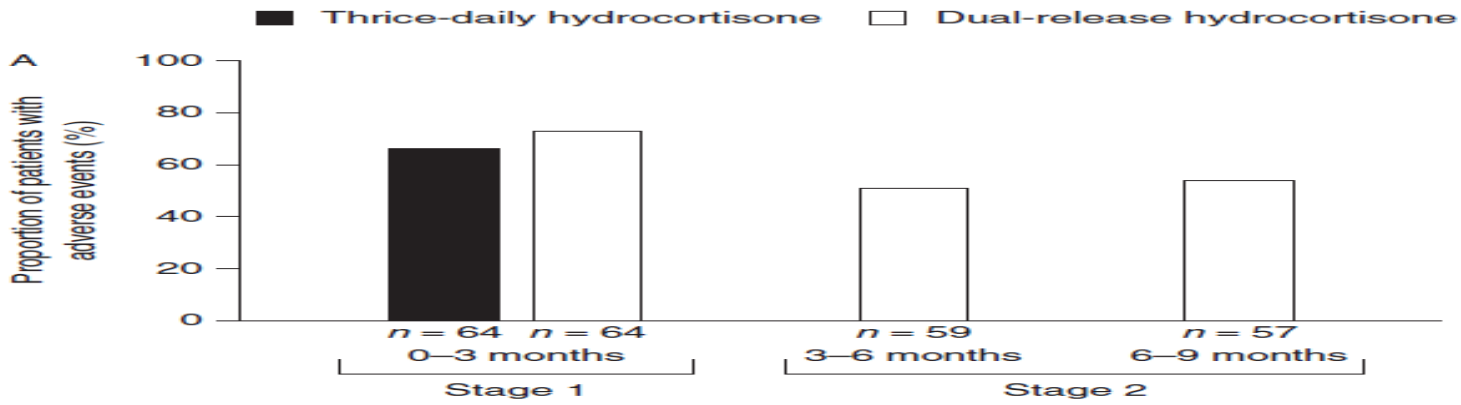


Table 3 Summary of adverse events during the first 18 months of stage 3; includes 55 patients who entered stage 3 from stages 1 and 2 and 16 new patients.

	0–6 months (n=71)		**6–12 months** (n=68)		**12–18 months** (n=68)		**0–18 months** (n=71)	
	Events	Patients with ≥1 event, n (%)	Events	Patients with ≥1 event, n (%)	Events	Patients with ≥1 event, n (%)	Events	Patients with ≥1 event, n (%)
Adverse events	136	53 (74.6%)	79	44 (64.7%)	107	50 (73.5%)	322	68 (95.8%)
Serious adverse events	6	6 (8.5%)	4	3 (4.4%)	5	4 (5.9%)	15	10 (14.1%)
Discontinuation because of an adverse event	2	2 (2.8%)	0	0	1	1 (1.4%)	3	3 (4.2%)
Adverse events occurring in ≥10% of patients during 18 months of follow-up								
Nasopharyngitis	28	16 (22.5%)	18	14 (20.6%)	21	15 (22.1%)	67	31 (43.7%)
Fatigue	5	5 (7.0%)	6	6 (8.8%)	11	6 (8.8%)	22	15 (21.1%)
Gastroenteritis	11	10 (14.1%)	3	3 (4.4%)	5	5 (7.4%)	19	15 (21.1%)
Headache	11	11 (15.5%)	5	3 (4.4%)	2	2 (2.9%)	18	14 (19.7%)
Vertigo	7	6 (8.5%)	2	2 (2.9%)	3	3 (4.4%)	12	10 (14.1%)
Pyrexia	4	4 (5.6%)	3	3 (4.4%)	3	3 (4.4%)	10	9 (12.7%)
Arthralgia	1	1 (1.4%)	3	3 (4.4%)	5	5 (7.4%)	9	9 (12.7%)

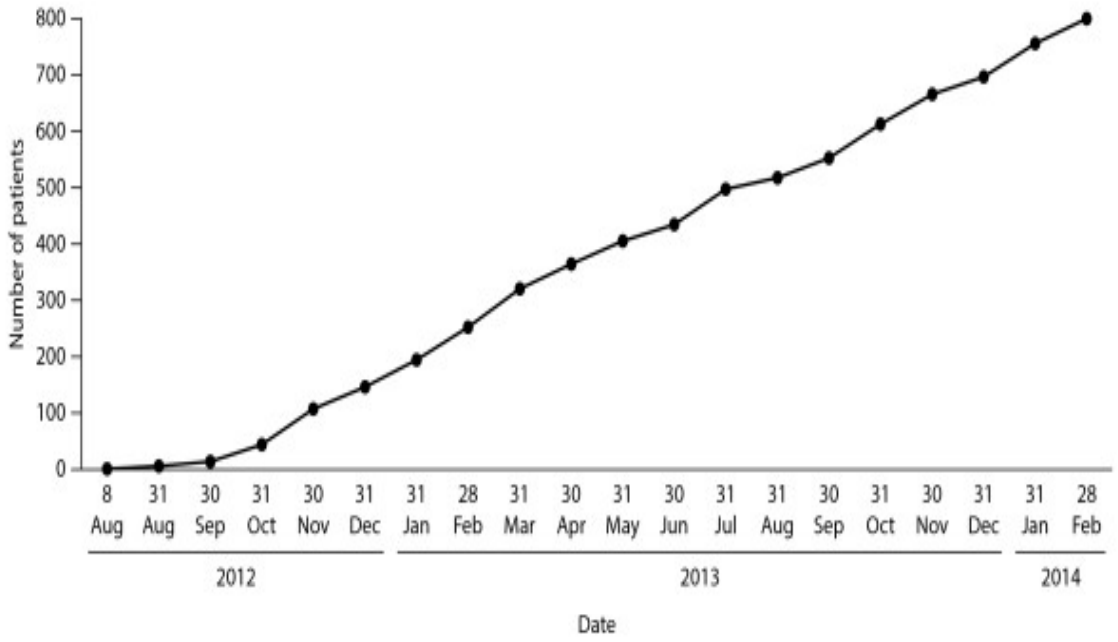
European Journal of Endocrinology (2014) **171**, 369–377

BMC Endocr Disord. 2014 May 9;14:40. doi: 10.1186/1472-6823-14-40.

European Adrenal Insufficiency Registry (EU-AIR): a comparative observational study of glucocorticoid replacement therapy.

Ekman B, Fitts D[1], Marelli C, Murray RD, Quinkler M, Elisse PM

Cumulative numbers of patients enrolled in EU-AIR since August 2012



Ricerca del giusto equilibrio

Sovra- dosaggio:

- S. Cushing iatrogena
- Aumentato rischio CV
- Infezioni

Sotto- dosaggio:

- Segni di ipofunzione
- Crisi iposurrenalica

Sintomi indicativi di sotto- o sovratrattamento

Indicativi di sottotrattamento	Indicativi di sovratrattamento
Affaticamento	Insonnia
Perdita di energia	Infezioni ricorrenti
Riduzione delle forze	Lombalgia
Dolore muscolare	Aumento dell'appetito
Nausea	Obesità addominale
Calo ponderale (> 3 kg)	Aumento ponderale (> 3 kg)
Iperpigmentazione	Edema periferico
Glicemia a digiuno < 3,3 mmol/l, sintomi di ipoglicemia	Glicemia a digiuno > 5,6 mmol/l
Riduzione del sodio sierico o aumento del potassio sierico	Aumento del sodio sierico o riduzione del potassio sierico
Pressione arteriosa (da seduto): pressione arteriosa sistolica <100 mmHg, pressione arteriosa diastolica <60 mmHg	Pressione arteriosa (da seduto): pressione arteriosa sistolica >140 mmHg, pressione arteriosa diastolica >90 mmHg

Non c'è un esame biochimico affidabile per valutare l'adeguatezza della terapia sostitutiva con GC

- **ACTH**
- **Cortisoluria 24 h**
- **Curva di cortisolo sierico**
- **Profilo di cortisolo salivare:**

➢ **Singolo dosaggio di cortisolo dopo 4 ore dalla terapia (e confronto con normogramma)**

➢ **« Hair cortisol »**

1. **Ricerca segni clinici di sovra –sottodosaggio GC/MC**

2. **Valutazione della QoL**

Valutazione di:

→ **PAOS, Peso, BMI, waist**

→ Na+, K+; PRA (DRC)→ normale o ai limiti superiori

→ **Glicemia/OGTT, calcolo rischio CV**

DEXA/Rx colonna: ↑ rischio osteoporosi se HC > 25-30 mg/die

Terapia con GC:

- **Sotto-dosata**: ↓ peso, astenia, nausea, mialgie….
- **Sovra-dosata**: ↑ peso, obesità centrale, IGT/DM, osteoporosi ecc…

- **Valutazione della QoL (questionario specifico: AddiQol).**

Nell'Addison, specie quando la terapia non sembra adeguata, considerare anche la coesistenza/insorgenza di altre patologie autoimmuni…

- **TSH** (dosaggio annuale per screening tireopatia,)
- **Emocromo** (per valuatare anemia perniciosa, celiachia..)

Considerare Sindrome Poliendocrina Autoimmune….

Dosi più basse e aggiustamenti in funzione delle altre terapie ormonali concomitanti

Paziente con Addison e ipertensione:

- Indicata restrizione sodica e riduzione della dose di fludrocortisone

- **Il Fludrocortisone non deve esser sospeso** (rischio di deplezione Na+)

Se è indicata una terapia con antiipertensivi, non usare diuretici e spironolattone. Meglio calcioantagonisti.

NB: HC ha anche effetto MC: generalmente la dose di Fludrocortisone va ridotta (0.05 mg die o anche meno in alcuni casi).

Con Prednisone 7.5 mg o Dex, generalmente la dose di MC va aumentata

Se la terapia con GC non è adeguata :

- Modificare dosi
- Cambiare il numero di somministrazioni /die
- Cambiare la formulazione del GC usato

Clinical Endocrinology (2012) 76, 21–25

CLINICAL QUESTION

What is the best long-term management strategy for patients with primary adrenal insufficiency?

Marcus Quinkler* and Stefanie Hahner†

Special conditions

❖ Very high body temperature (> 40°C)

✓ triplicate replacement therapy

❖ Vomiting or diarrhoea

✓ hydrocortisone 50 mg im twice daily

❖ Low-grade fever

❖ Intercurrent acute diseases

✓ Duplicate replacement therapy

✧ Modified release hydrocortisone

✓ Morning administration + duplicate or triplicate maintenance doses *die* with intervals of 8 ± 2 hours

Other conditions?

- work-related stress
- psychophysical stress
- seasonal changes
- melancholy or depression
- insomnia
- altering light-dark rhythm

- vomito 33%
- diarrea 23%
- influenza 11%
- infezioni maggiori 6%
- chirurgia 6%
- perdita di coscienza 6%
- dolore acuto 4%
- shock 4%
- altro 3%
- affaticamento/terapia inadeguata 2%
- non note 1%
- stress ansia 1%

European Journal of Endocrinology (2010) **162** 115–120

Clinical Endocrinology (2012) 76, 21–25

CLINICAL QUESTION

What is the best long-term management strategy for patients with primary adrenal insufficiency?

Marcus Quinkler* and Stefanie Hahner†

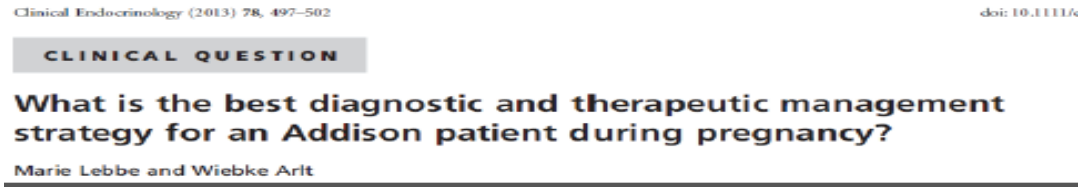
- ✧ Additional dose of hydrocortisone (5-10 mg)

  in cases of psycho-physical stress

- ✧ Increase the fludrocortisone dose (0.1-0.2 mg/die) in case of hot climate

Pregnant patients

- Due to the physiological increase in free cortisol during late pregnancy, PAI women should receive a 20–40% increase in hydrocortisone dose between second and third trimester.
- Fludrocortisone dose does not require routine adjustment, but adequacy of dose should be monitored by postural blood pressure and serum electrolytes. Renin is not a valid indicator of mineralocorticoid requirements as it physiologically increases during pregnancy.
- Peripartum management includes the initiation of parenteral administration of hydrocortisone in doses recommended for major surgical stress (50–100 mg hydrocortisone every 6–8 h), which should be initiated at the onset of the active phase of labour or prior to planned Caesarean section.
- After delivery, hydrocortisone dose can be quickly tapered to prepregnancy levels if all is well.


Clinical Endocrinology (2013) 78, 497–502 doi: 10.1111/

CLINICAL QUESTION

What is the best diagnostic and therapeutic management strategy for an Addison patient during pregnancy?

Marie Lebbe and Wiebke Arlt

Dose adjustment in surgical interventions

- Major surgery or intensive care

Cortisol secretion rate in response to general anaesthesia

ranges between 75 – 150 mg/die

Ann Surg '94;219:416-425
Endocrinol Metab North Am '03,32.367-383

Recommended dose:

- hydrocortison 150 mg i.v. in continuous infusion in the first 24 hours
- hydrocortison 100 mg i.v. in infusion
- hydrocortison *per os* subsequently

BP&RCE&M '09;23:167-169

Endocrine (2013) 43:514–528
DOI 10.1007/s12020-012-9835-4

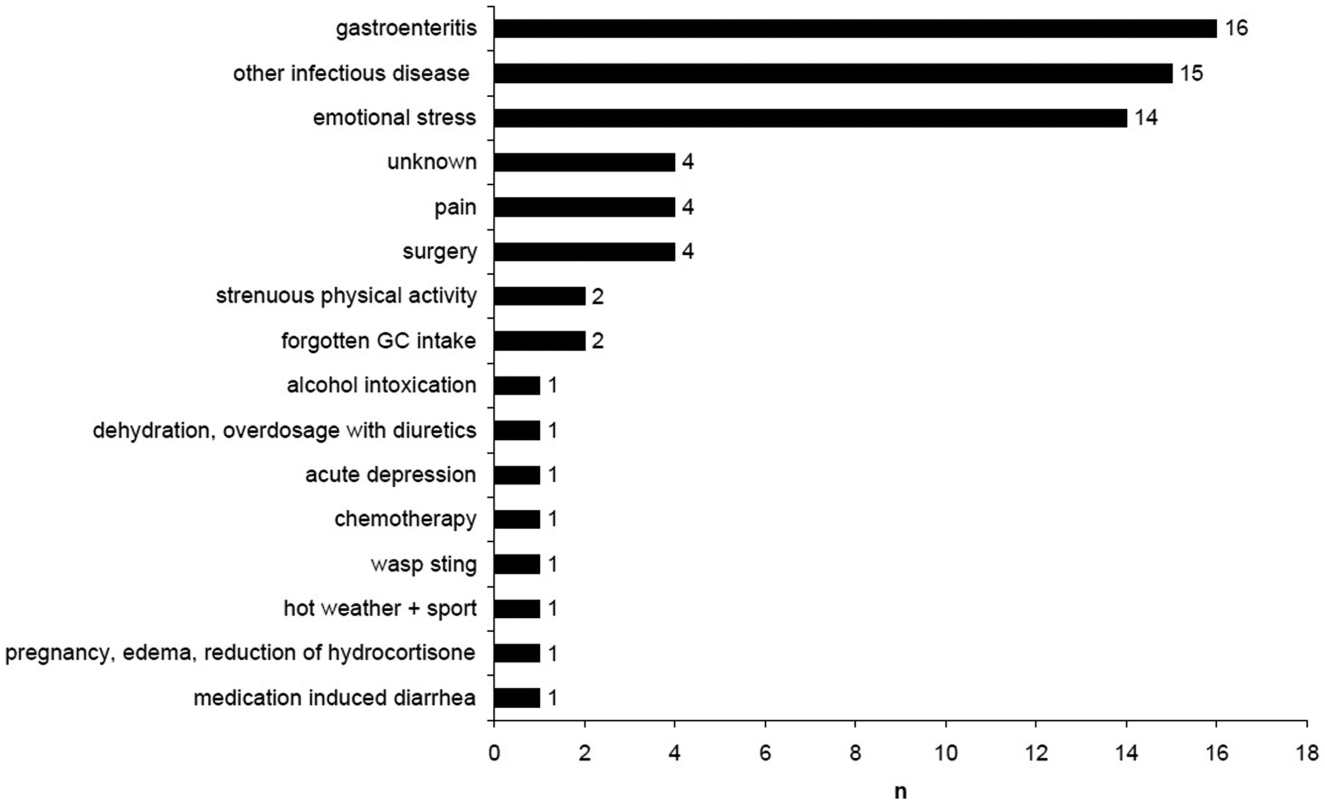
REVIEW

Therapy of adrenal insufficiency: an update

Alberto Falorni · Viviana Minarelli · Silvia Morelli

Table 4 Doses of hydrocortisone in the case of surgical interventions

Type of surgery	Pre-surgery	Post-surgery
Major surgery with general anaesthesia	i.v. or i.m. 100 mg before anaesthesia	i.v. infusion of 300 mg in 2–3 l saline in the first 24 h i.v. or i.m. 100 mg × 2 the 2nd day and 50 mg × 2 the 3th day Double oral dose the 4th and 5th day and subsequent progressive tapering
Minor surgery with general anaesthesia	i.m. 100 mg before anaesthesia	Double oral dose for 48 h Subsequent progressive tapering
Local anaesthesia	Not required	Double oral dose for 24 h after surgery
Major dental surgery with general anaesthesia	i.m. 100 mg before anaesthesia	Double oral dose for 48 h Subsequent progressive tapering
Minor dental surgery with local anaesthesia	Double oral dose before surgery	Double oral dose for 24 h



J Clin Endocrinol Metab. 2015 Feb;100(2):407-16. doi: 10.1210/jc.2014-3191. Epub 2014 Nov 24.

High incidence of adrenal crisis in educated patients with chronic adrenal insufficiency: a prospective study.

Hahner S[1], Spinnler C, Fassnacht M, Burger-Stritt S, Lang K, Milovanovic D, Beuschlein F, Willenberg HS, Quinkler M, Allolio B

Durante tutto lo studio si sono verificate 64 crisi surrenaliche **(8.3/100 pazienti-anno), fatali nel 6.3% dei casi**.

I sintomi riportati con maggior frequenza sono stati astenia (74%), nausea (57%), vomito (52%), diarrea (45%), alterazioni PA (22%) e algie addominali (22%).

I **fattori di rischio** per AC sono stati maggior durata di malattia, sesso femminile e PAI.

Una precedente AC si associa maggiormente con il rischio di un nuovo episodio durante il *follow-up* (OR 2.9).

I **fattori precipitanti** più frequenti sono risultati soprattutto gastro-enteriti (34%), altre malattie infettive (32%) e *stress* emotivo (30%), seguiti in percentuali minori da dolore intenso, intervento chirurgico, attività fisica intensa, dimenticanza dell'assunzione della terapia, intossicazione da alcool, disidratazione o sovradosaggio diuretici, depressione, chemioterapia, puntura d'insetto, gravidanza con stato edematoso e riduzione della terapia, diarrea iatrogena.

Published in: Stefanie Hahner; ; Marcus Quinkler; Bruno Allolio et al.; ***The Journal of Clinical Endocrinology & Metabolism*** **2015, 100, 407-416.**
DOI: 10.1210/jc.2014-3191

Table 7 *Treatment of acute adrenal insufficiency*

Treatment	Dose/procedure
Hydrocortisone	100 mg bolus given immediately followed by 100–300 mg day^{-1} as continuous infusion or frequent intravenous or intramuscular boluses every 6 h
Intravenous substitution of fluids	3–4 L isotonic saline or 5 per cent dextrose in isotonic saline with an initial infusion rate of approximately 1 L h^{-1}; frequent hemodynamic monitoring and measurement of serum electrolytes to avoid fluid overload
Depending on the severity of the intercurrent illness	Admission to the intensive care or high-dependency unit; prophylaxis of gastric stress ulcer; low-dose heparin; antibiotic treatment

Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline

Stefan R. Bornstein (chair), Bruno Allolio, Wiebke Arlt, Andreas Barthel, Andrew Don-Wauchope, Gary D. Hammer, Eystein S. Husebye, Deborah P. Merke, M. Hassan Murad, Constantine A. Stratakis, and David J. Torpy*

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 Weight-appropriate continuous iv fluids with 5% dextrose and 0.2 or 0.45% NaCl Rapid tapering and switch to oral regimen depending on clinical state
Acute adrenal crisis	Rapid infusion of 1000 mL isotonic saline within the first hour or 5% glucose in isotonic saline, followed by continuous iv isotonic saline guided by individual patient needs Hydrocortisone 100 mg iv immediately followed by hydrocortisone 200 mg/d as a continuous infusion for 24 h, reduced to hydrocortisone 100 mg/d the following day Children, rapid bolus of normal saline (0.9%) 20 mL/kg. Can repeat up to a total of 60 mL/kg within 1 h for shock. Children, hydrocortisone 50–100 mg/m^2 bolus followed by hydrocortisone 50–100 mg/m^2/d divided q 6 h For hypoglycemia: dextrose 0.5–1 g/kg of dextrose or 2–4 mL/kg of D25W (maximum single dose 25 g) infused slowly at rate of 2 to 3 mL/min. Alternatively, 5–10 mL/kg of D10W for children <12 y old Cardiac monitoring: Rapid tapering and switch to oral regimen depending on clinical state

Abbreviation: D10W, 10% dextrose solution; D25W, 25% dextrose solution. [Adapted from B. Allolio: Extensive expertise in endocrinology: adrenal crisis. *Eur J Endocrinol.* 2015;172:R115–R124 (126), with permission. © Endocrine Society.]

Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline

Stefan R. Bornstein (chair), Bruno Allolio, Wiebke Arlt, Andreas Barthel, Andrew Don-Wauchope, Gary D. Hammer, Eystein S. Husebye, Deborah P. Merke, M. Hassan Murad, Constantine A. Stratakis, and David J. Torpy*

3.2 We suggest using hydrocortisone (15–25 mg) or cortisone acetate (20–35 mg) in two or three divided oral doses per day; the highest dose should be given in the morning at awakening, the next either in the early afternoon (2 h after lunch; two-dose regimen) or at lunch and afternoon (three-dose regimen). Higher frequency regimens and size-based dosing may be beneficial in individual cases. (2|⊕⊕◯◯)

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|⊕◯◯◯)

3.4 We suggest against using dexamethasone for the treatment of PAI because of risk of Cushingoid side effects due to difficulties in dose titration. (2|⊕⊕◯◯)

3.5 We suggest monitoring glucocorticoid replacement using clinical assessment including body weight, postural blood pressure, energy levels, signs of frank glucocorticoid excess. (2|⊕⊕⊕◯)

3.6 We suggest against hormonal monitoring of glucocorticoid replacement and to adjust treatment only based on clinical response. (2|⊕⊕⊕◯)

5.7-10 mg/m^2 production rate

15–25 mg hydrocortison = 25–37.5 mg cortone acetato

Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline

Stefan R. Bornstein (chair), Bruno Allolio, Wiebke Arlt, Andreas Barthel, Andrew Don-Wauchope, Gary D. Hammer, Eystein S. Husebye, Deborah P. Merke, M. Hassan Murad, Constantine A. Stratakis, and David J. Torpy*

Mineralocorticoid replacement in PAI

3.7 We recommend that all patients with confirmed aldosterone deficiency receive mineralocorticoid replacement with fludrocortisone (starting dose, 50–100 μg in adults) and not restrict their salt intake. (1|⊕⊕⊕⊕)

3.8 We recommend monitoring mineralocorticoid replacement primarily based on clinical assessment (salt craving, postural hypotension, or edema), and blood electrolyte measurements. (1|⊕⊕⊕◯)

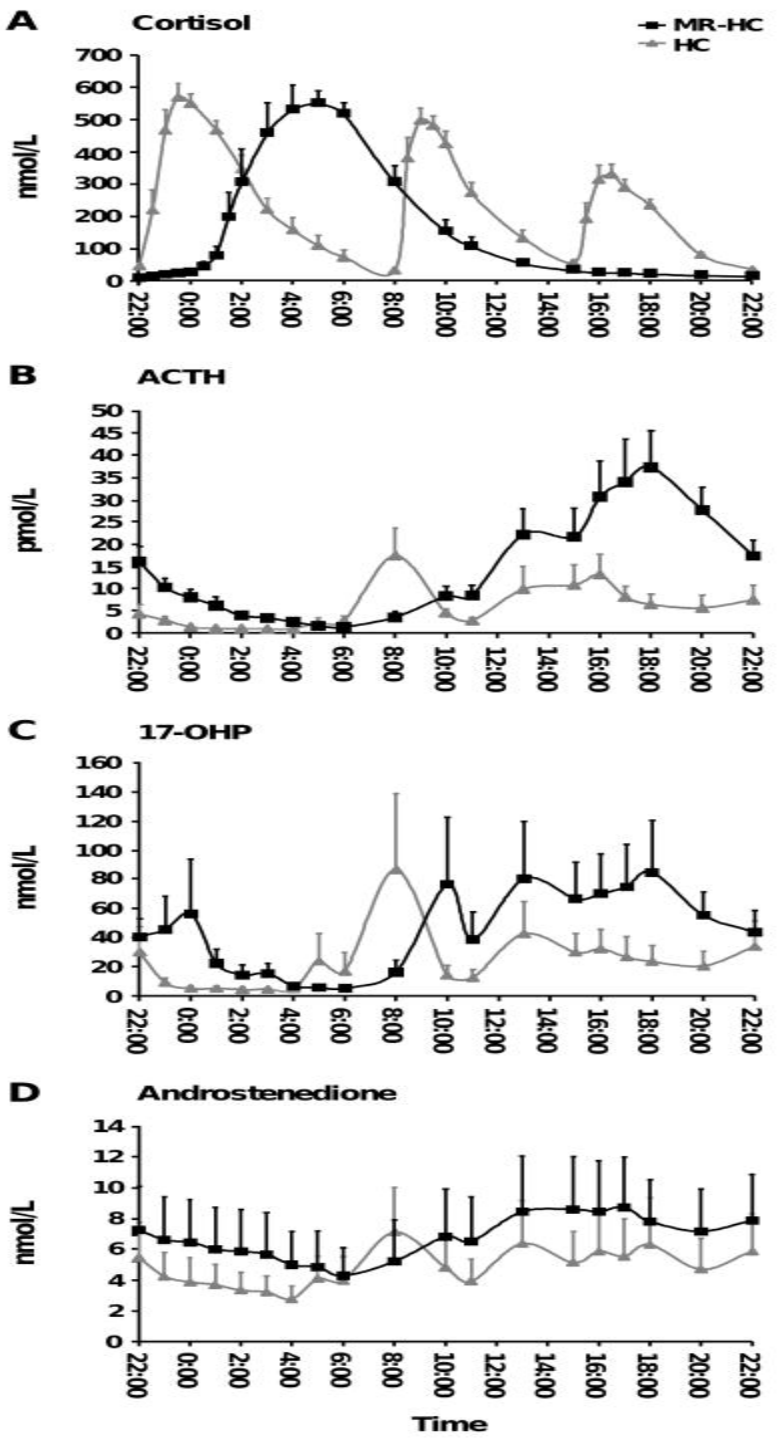
3.9 In patients who develop hypertension while receiving fludrocortisone, we suggest reducing the dose of fludrocortisone. (2|⊕◯◯◯)

3.10 If blood pressure remains uncontrolled, we suggest initiating antihypertensive treatment and continuing fludrocortisone. (2|⊕◯◯◯)

Clin Endocrinol (Oxf). 2010 Apr;72(4): 441-7. doi: 10.1111/j. 1365-2265.2009.03636.x. Epub 2009 May 25.

A pharmacokinetic and pharmacodynamic study of delayed- and extended-release hydrocortisone (Chronocort) vs. conventional hydrocortisone (Cortef) in the treatment of congenital adrenal hyperplasia.

Verma S[1], Vanryzin C, Sinaii N, Kim MS, Nieman LK, Ravindran S, Calis KA, Arlt W, Ross RJ, Merke DP.



J Clin Endocrinol Metab. 2014 Dec 11:jc20143809. [Epub ahead of print]

A Phase 2 Study of Chronocort®, a Modified-release Formulation of Hydrocortisone, in the Treatment of Adults with Classic Congenital Adrenal Hyperplasia.

Mallappa A[1], Sinaii N, Kumar P, Whitaker MJ, Daley LA, Digweed D, Eckland DJ, VanRyzin C, Nieman LK, Arlt W, Ross RJ, Merke DP.

Conclusions: Twice daily Chronocort® approximates physiologic cortisol secretion, and was well tolerated and effective in controlling androgen excess in adults with CAH. This novel hydrocortisone formulation represents a new treatment approach for patients with CAH.

E allora,quale farmaco usare?.....

Chiedetelo anche al vostro Direttore Generale !


Thank You!