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ITALIAN CHAPTER

17° Congresso Nazionale AME

Joint Meeting with AACE Italian Chapter

Update in Endocrinologia Clinica

8-11 novembre 2018

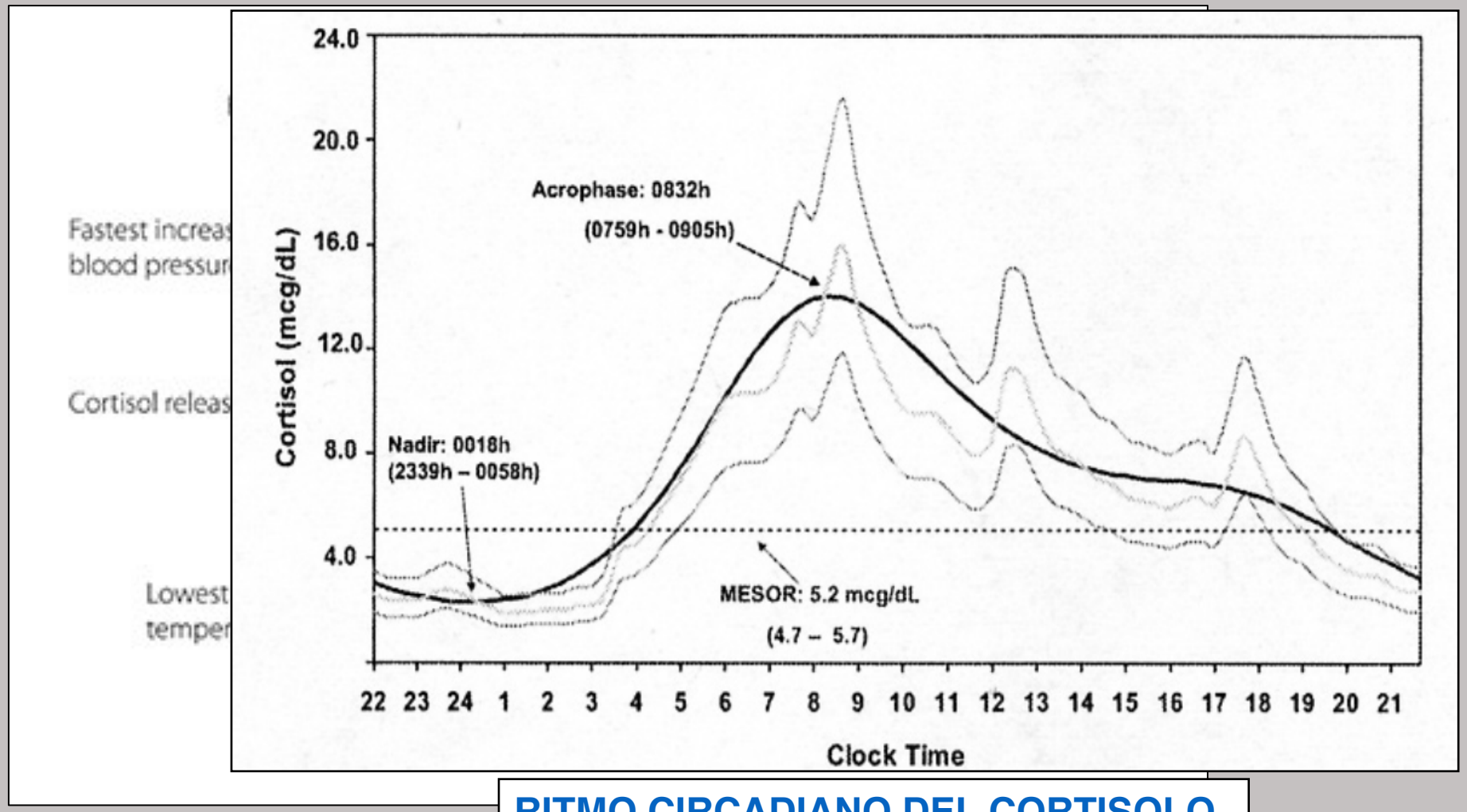
Roma

Iposurrenalismo primitivo e secondario
Criteri diagnostici ed aree grigie

Stefano Laureti

Magione (Perugia) USL 1 Umbria

Biological clock

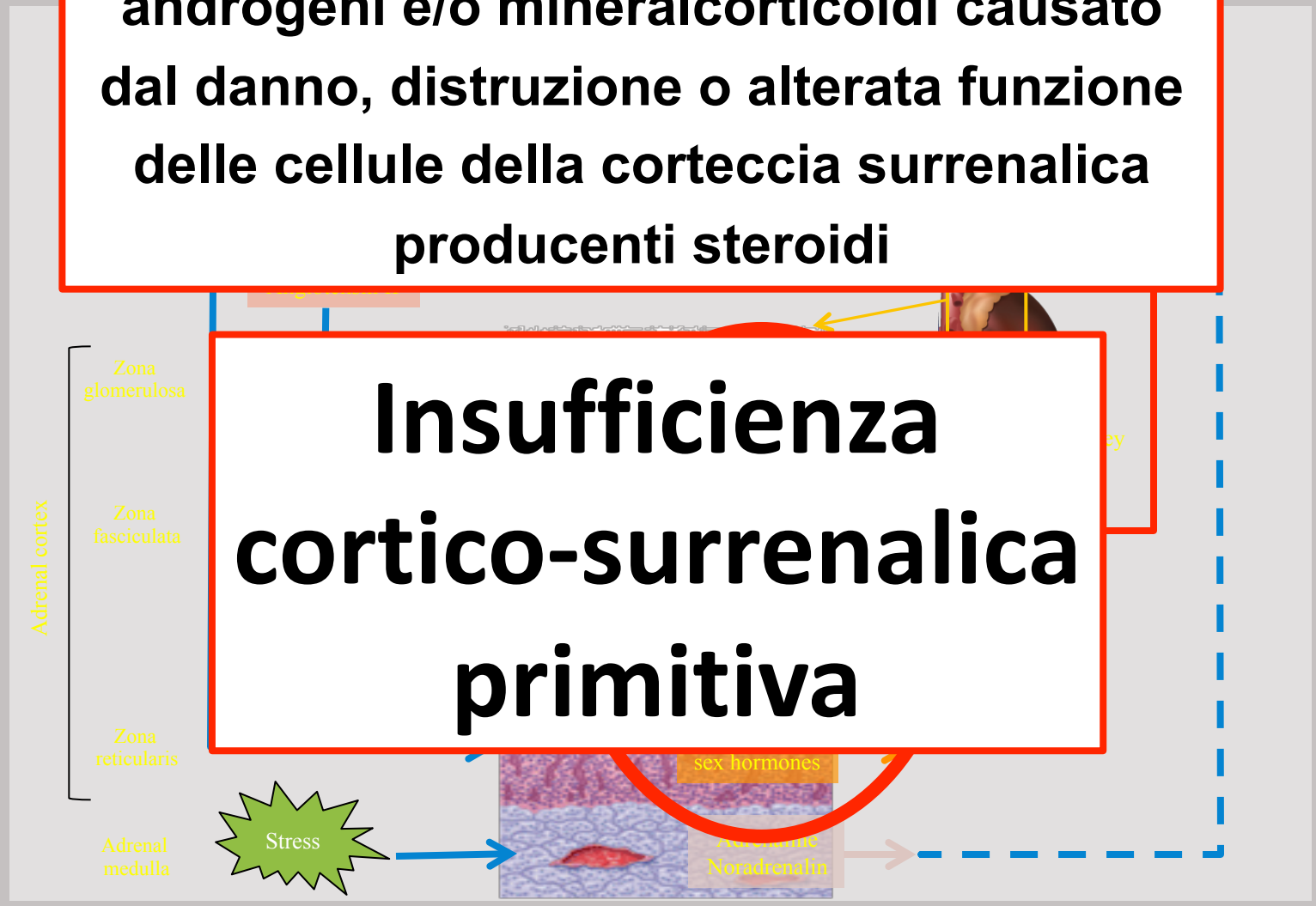


RITMO CIRCADIANO DEL CORTISOLO

The circadian clock anticipates and adapts our physiology to the different phases of the day.

The HPA axis and normal adrenal function

Deficit secretivo di glucocorticoidi, androgeni e/o mineralcorticoidi causato dal danno, distruzione o alterata funzione delle cellule della corteccia surrenalica producenti steroidi



Insufficienza cortico-surrenalica primitiva

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Insufficienza cortico-surrenalica primitiva
PREVALENZA

✓35–60/milione (Mason AS, Lancet II. 1968; Nerup J., Acta Endocrinol 1974) UK e Danimarca

✓93/milione (Willis AC., Postgrad Med. J. 1997) UK

✓110/milione (Kong MF., Clin Endocrinol. 1994) UK

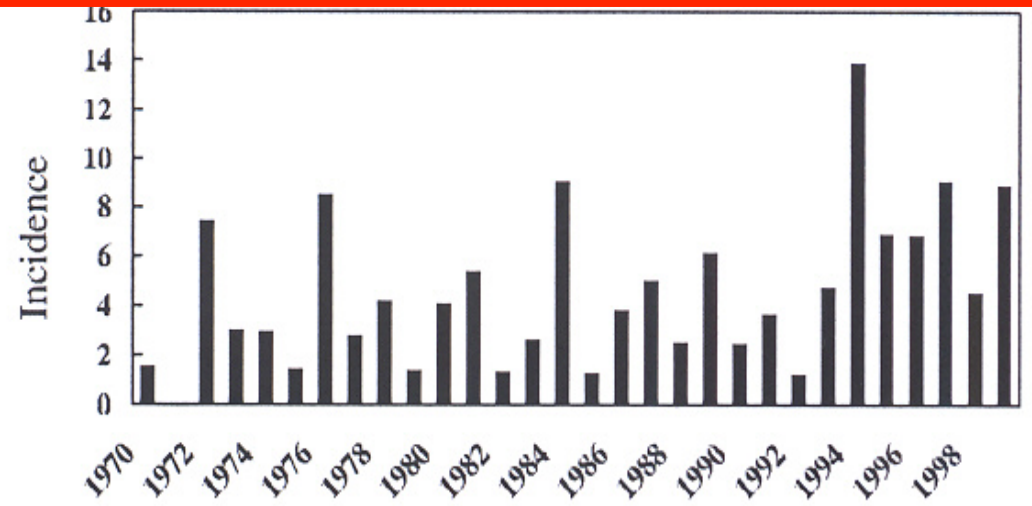
117 casi/milione (95% CI: 95-143)

(1 caso ogni 8.500 persone) (Umbria-Italia)

Prevalenza in maschi:106/milione (95% CI: 77-144)
Prevalenza in femmine: 127/milione (95% CI: 95-166)
Grado di accertamento: 97%
(Capture/recapture analysis)
Laureti S. et al JCEM 1999

High prevalence and increasing incidence of Addison's disease in western Norway (Løvas & Husebye Clin. Endocrinology 2002)

Prevalence: 140 cases/milion inhabitants
(1 case every 7,150 persons)
Mean Incidence: 0.62/100.000/year



ALMENO 100.000 PAZIENTI CON INSUFFICIENZA CORTICOSURRENALICA PRIMITIVA

ALMENO 8.000 PAZIENTI CON INSUFFICIENZA CORTICOSURRENALICA PRIMITIVA

MEDIAMENTE 1 NUOVO CASO DI INSUFFICIENZA CORTICOSURRENALICA PRIMITIVA AL GIORNO

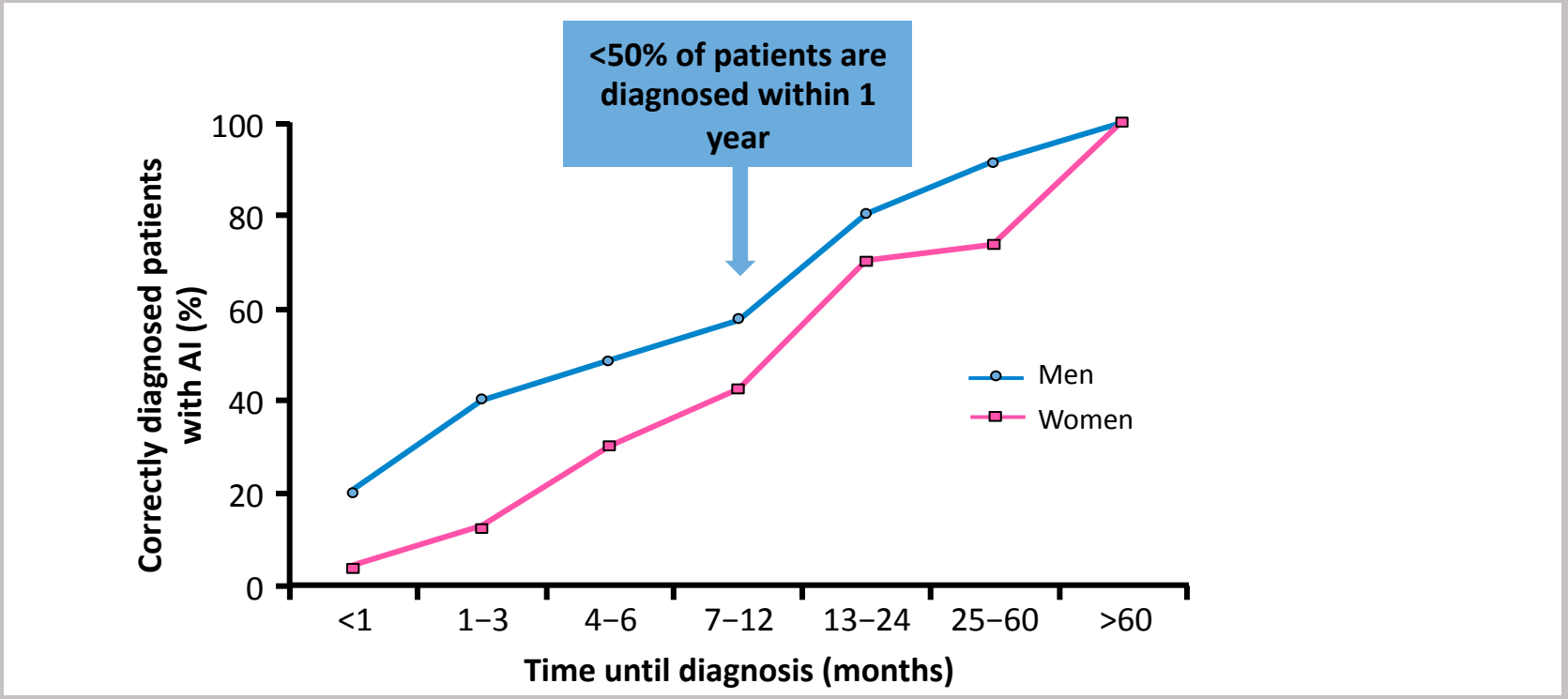
Signs and symptoms of chronic adrenal insufficiency[1]

Symptoms	Signs
• Fatigue, lack of stamina, reduced strength • Anorexia, weight loss • Gastric pain, nausea, vomiting • Myalgia, joint pain • Dizziness • Dry and itchy skin (in women) • Loss of libido (in women) • **Salt craving**	• Fever • Low blood pressure, postural hypotension • Hyponatraemia • Anaemia, lymphocytosis, eosinophilia • Hypoglycaemia • Loss of axillary or pubic hair (in women) • **Skin hyperpigmentation** • **↑ serum creatinine** • **Hyperkalaemia** • **Hypercalcaemia** • **Very pale skin**

Primary AI only
Secondary AI only

1. Arlt W and Allolio B. Lancet 2003;361:1881–1893

Delayed diagnosis of adrenal insufficiency is common in clinical practice[1]



- 67% of patients consulted ≥3 physicians before being correctly diagnosed
- 68% of patients incorrectly diagnosed initially
  - Psychiatric and gastrointestinal disorders most common incorrect diagnoses

Figure adapted from Bleicken et al. Reproduced bypermission.

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

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 1. Clinical Features of Adrenal Insuffi

Symptoms	Signs
Adrenal insufficiency	
Fatigue	Hyperpigme areas, ski breast
Weight loss	Low blood
Postural dizziness	Failure to th
Anorexia, abdominal discomfort	
Adrenal crisis	
Severe weakness	
Syncope	Hypotensio
Abdominal pain, nausea, vomiting; may mimic acute abdomen	Abdominal
Back pain	Reduced co
Confusion	

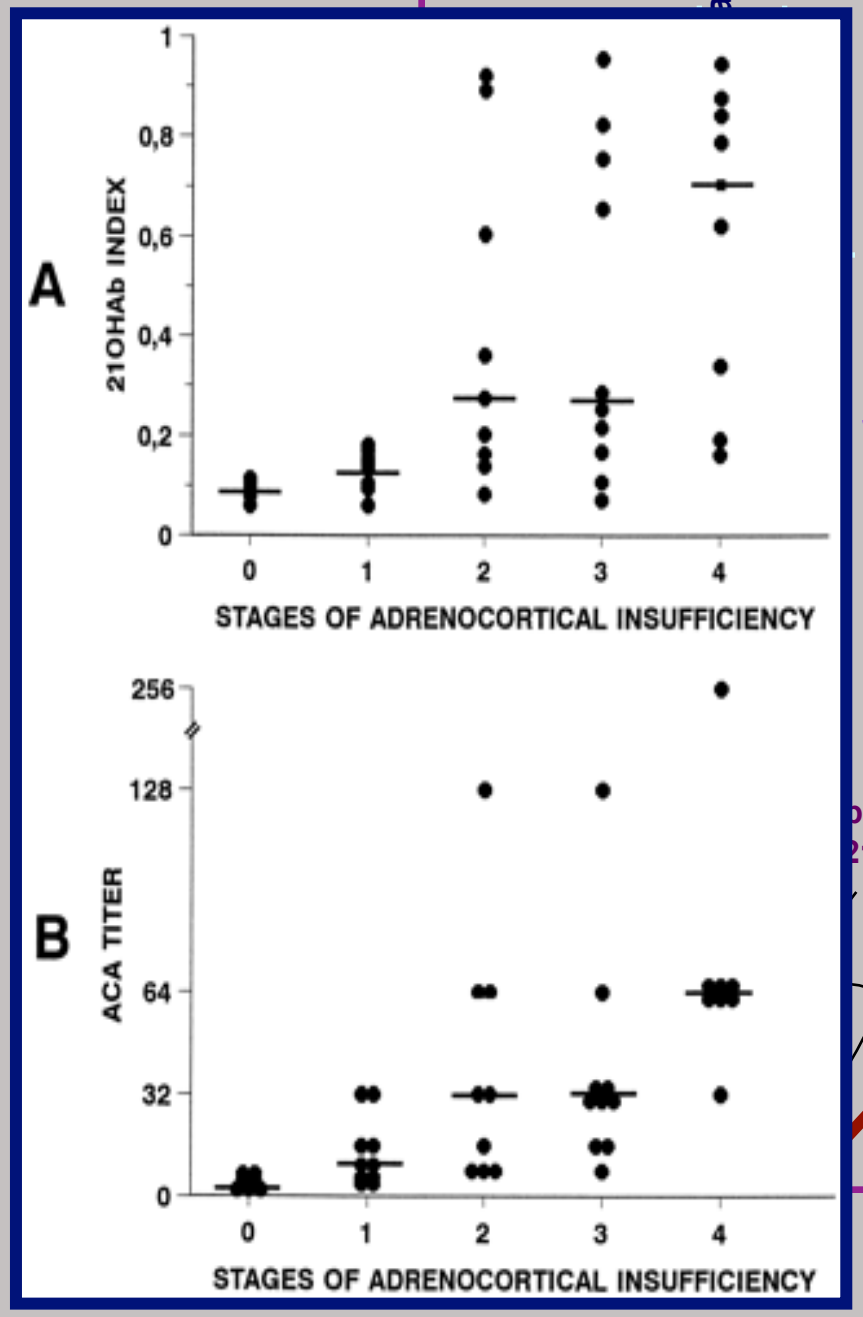
2.0 Optimal diagnostic tests

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

2.4 We recommend measurement of plasma ACTH to establish PAI. The sample can be obtained at the same time as the baseline sample in the corticotropin test or paired with the morning cortisol sample. In patients with confirmed cortisol deficiency, a plasma ACTH >2-fold the upper limit of the reference range is consistent with PAI. (1|⊕⊕⊕◯)

2.5 We recommend the simultaneous measurement of plasma renin and aldosterone in PAI to determine the presence of mineralocorticoid deficiency. (1|⊕⊕⊕◯)

Falorni A & Laureti S, The Endocrinologist, 2000



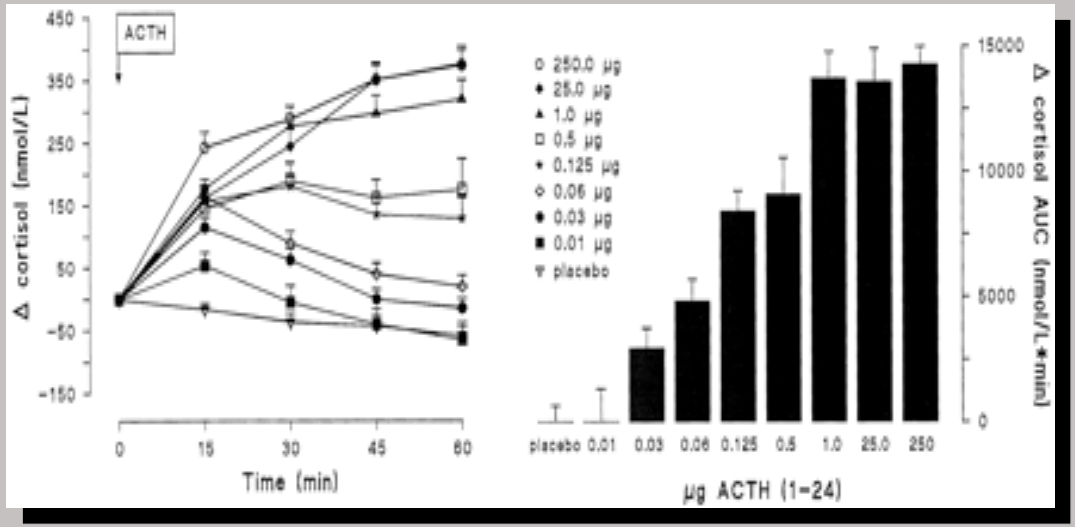
Insufficienza cortico-surrenalica
Pre-clinica
ACTH-test normale: 15% progressione
ACTH-test sub-normale: 90% progressione

Laureti S et al. JCEM 1998

Insufficienza cortico-surrenalica primitiva DIAGNOSI

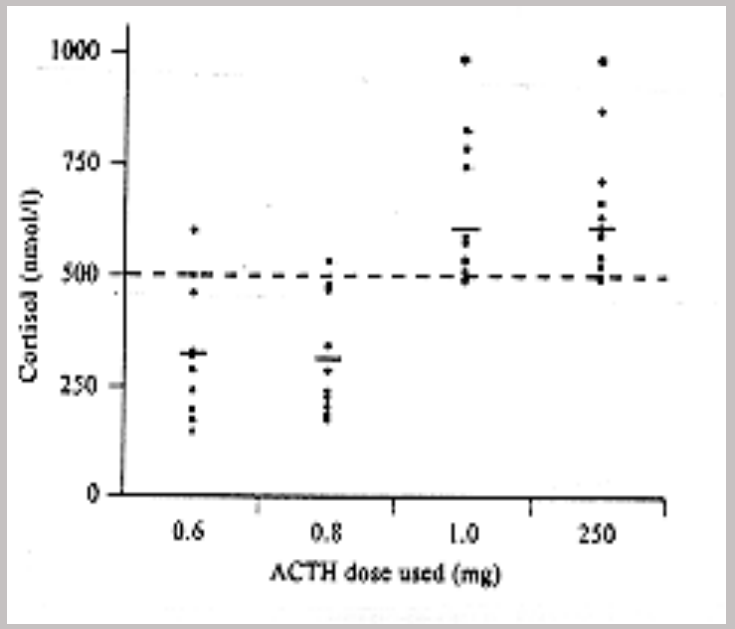
• ACTH basale	> 100 pg/ml
• Cortisolo basale	< 5 μg/dl
• Cortisolo dopo Synacthen 250 μg (HDT)	< 18.1-20 μg/dl
• Cortisolo dopo Synacthen 1 μg (LDT)	< 18.5 μg/dl
• Cortisolo basale (in acute illness)	< 9 μg/dl

The lowest dose of synthetic ACTH able to induce a maximal stimulation of the adrenal cortex is 1 μg (LDT test)

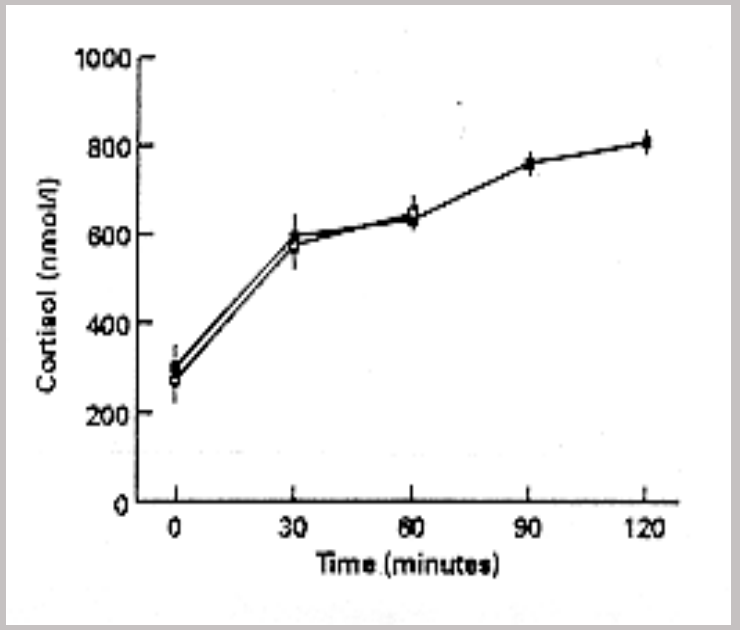


Arvat et al, JCEM 2000

Plasma concentration of cortisol after LDT and HDT



Dickstein G et al Eur J Endocrinol 1996



Laureti S et al Clin Endocrinol 2000

Table 2 *Classification and causes of primary adrenal insufficiency*

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

Review ● Journal of INTERNAL MEDICINE

doi: 10.1111/joim.12162

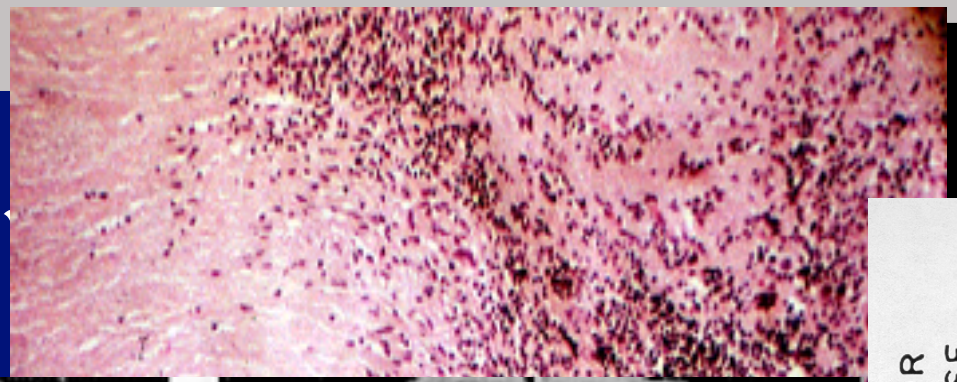
Consensus statement on the diagnosis, treatment and follow-up of patients with primary adrenal insufficiency

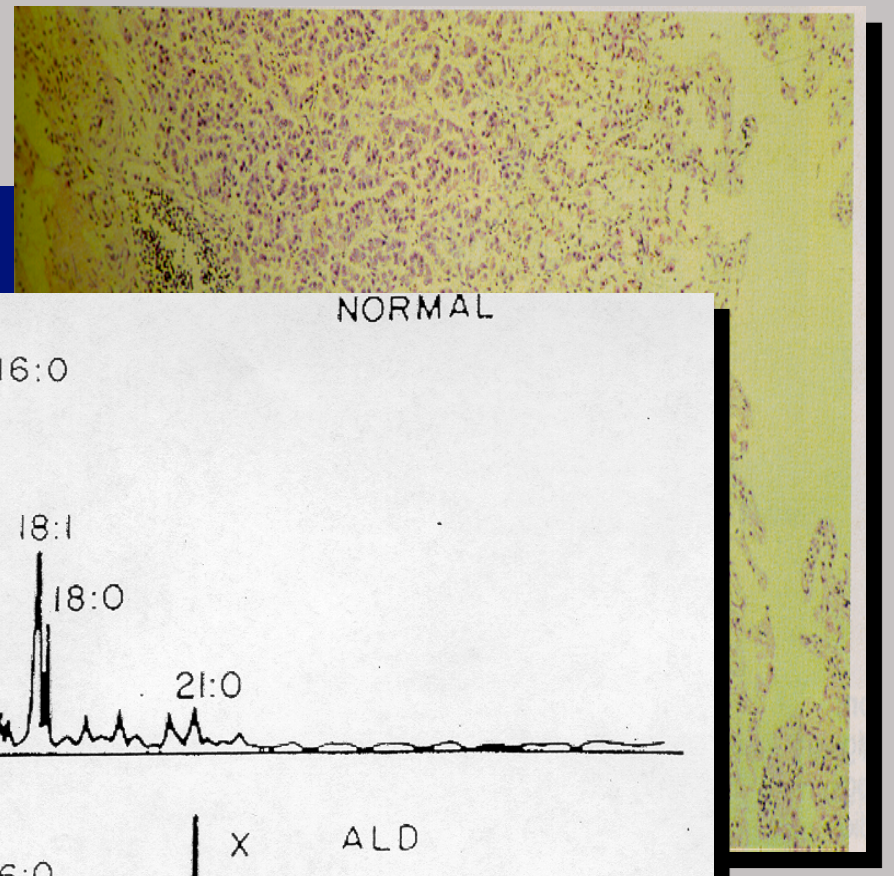
E. S. Husebye[1,2], B. Allolio[3], W. Arlt[4], K. Badenhoop[5], S. Bensing[6], C. Betterle[7], A. Falorni[8], E. H. Gan[9], A.-L. Hulting[6], A. Kasperlik-Zaluska[10], O. Kämpe[11], K. Løvås[1,2], G. Meyer[5] & S. H. Pearce[9]

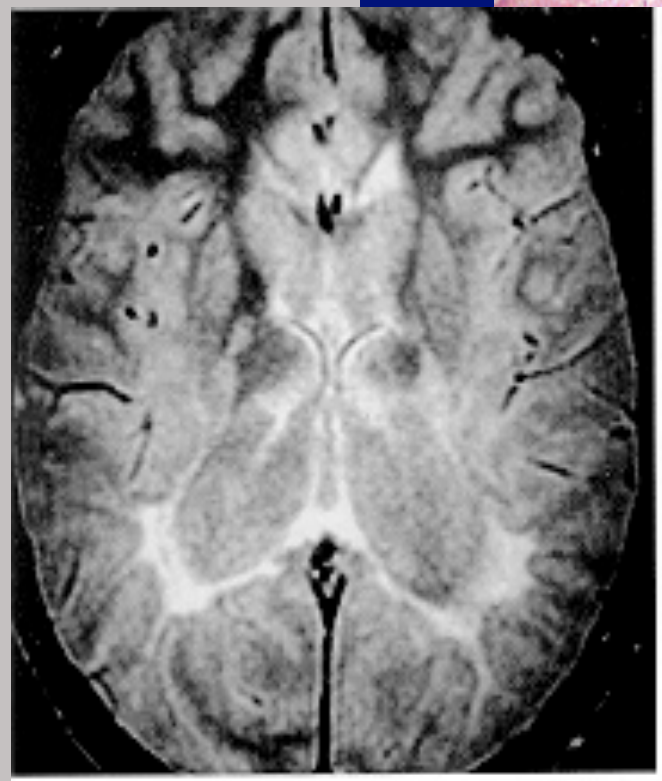
Insufficienza Corticosurrenalica Primitiva
CAUSE

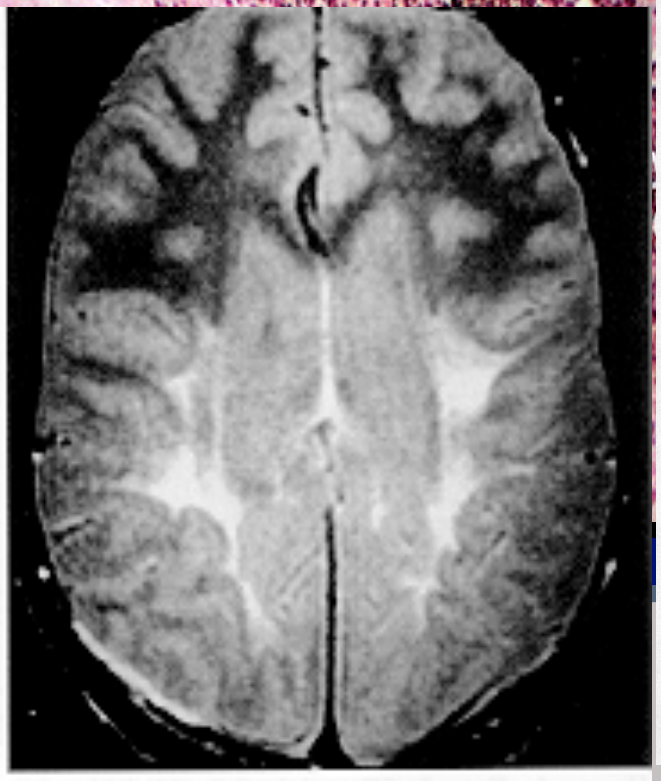
✓Autoimmune	80-85%
✓ Post-tubercolosi	10-15%
✓X-linked adrenoleucodistrofia	5-10%
✓ Forme rare	2-5%

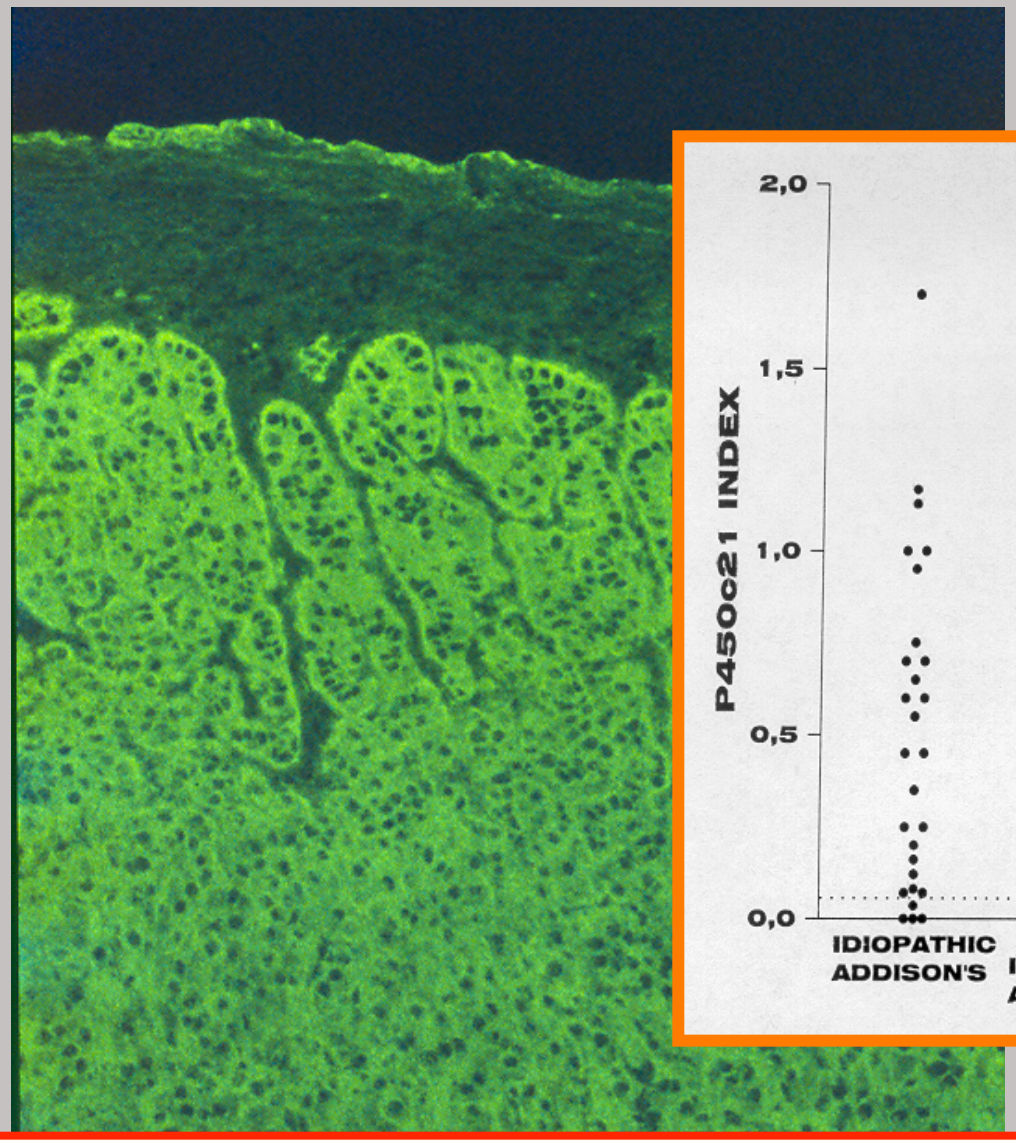
Insufficienza Corticosurrenalica Primitiva
CAUSE



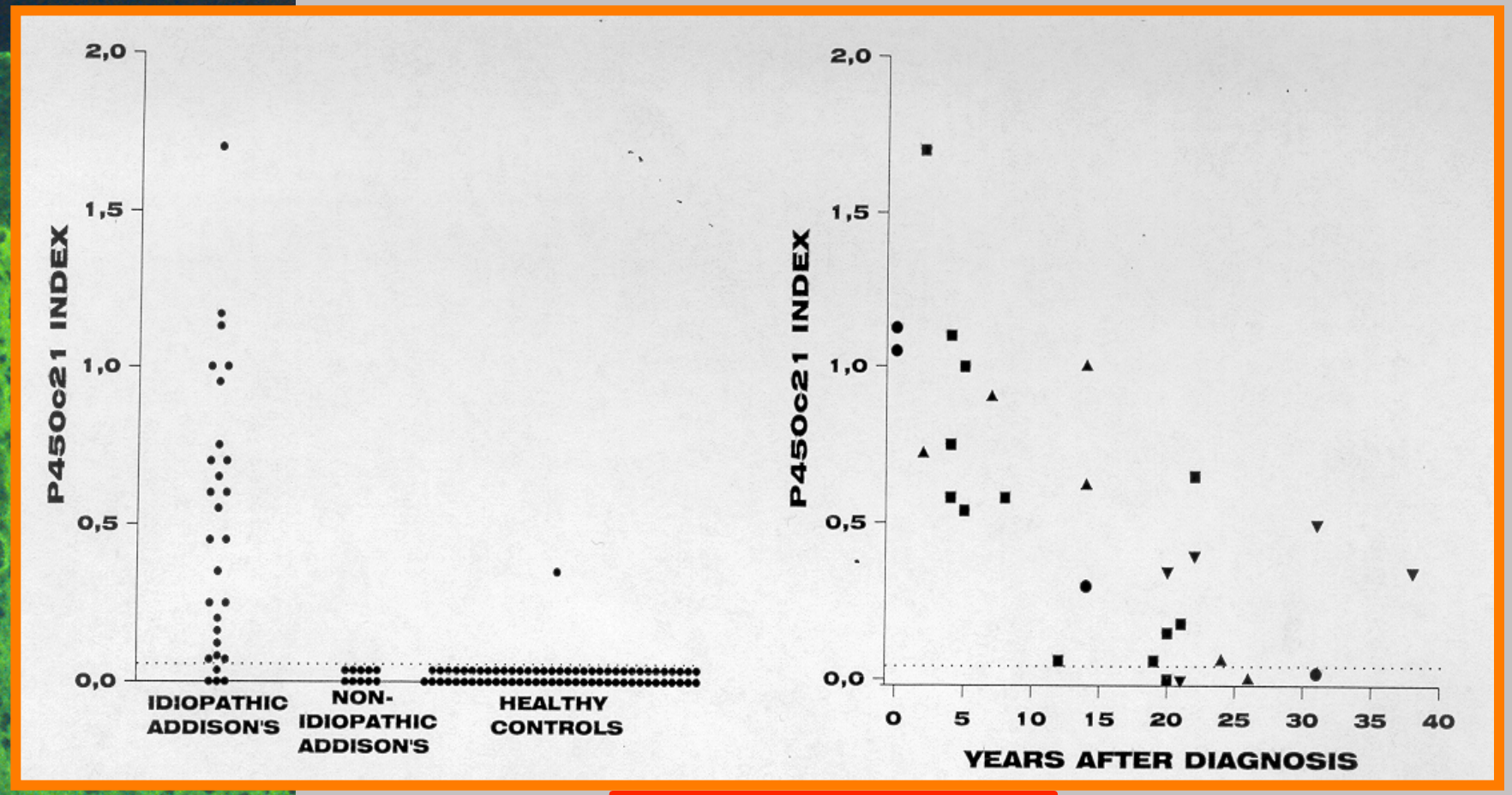








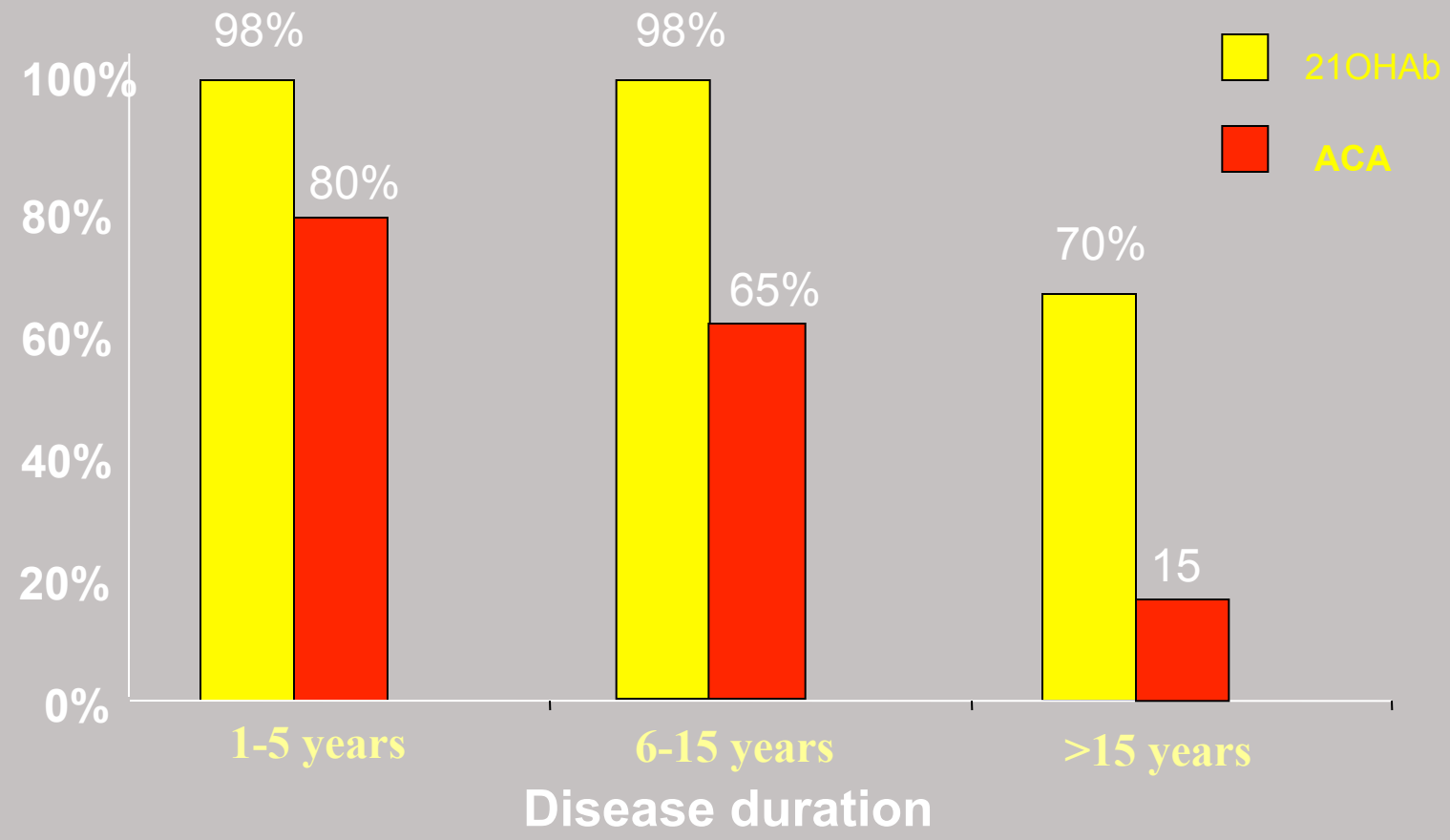
Adrenal cortex autoantibodies (ACA) determined by indirect immunofluorescence on cryostatic sections of adrenal gland



21OHAb in PAI

Falorni et al JCEM, 1995

Prevalence of 21OHAb and ACA in autoimmune PAI



Falorni et al, Clin Exp Immunol, 1997; Laureti et al. JCEM, 1998

INSUFFICIENZA CORTICO-SURRENALICA PRIMITIVA AUTOIMMUNE

Isolata

Sindrome poliendocrina tipo I

Sindrome poliendocrina tipo II

Sindrome poliendocrina autoimmune di tipo II (SPA II)

✓ Età insorgenza	Adulta
✓ Trasmissione genetica	Poligenica
	HLA DR3-DQ2; MICA 5.1
✓ Componenti endocrine	ICSP (100%)
	Tireopatie (60%)
	Diabete di tipo 1 (50%)
	Ipogonadismo (20%)
✓ Componenti extra-endocrine	Anemia perniciosa (0.5-1%)
	Vitiligine (4-5%)
	Alopecia (0.5-1%)
	Morbo celiaco (0.5-1%)

SENSIBILITA' E SPECIFICITA' DIAGNOSTICA DEI 21OHAb PER L'ICSP AUTOIMMUNE

Diagnosi	Sensibilità diagnostica	Specificità diagnostica
ICSP (idiopatica)	91,1% (44/48)	-
Adrenoleucodistrofia X-linked	-	100% (29/29)
ICSP post-TBC	-	100% (16/16)
Morbo di Basedow	-	99% (95/96)
Diabete mellito tipo 1	-	99,5% (193/194)
Tiroidite Hashimoto	-	100% (18/18)
Soggetti sani di controllo	-	99,5% (169/170)

Falorni A et al. JCEM, 1995 - Falorni A et al. Clin. Exp. Immunol., 1997
Laureti S et al Horm. Metab. Res., 1996. - Laureti et al. JCEM, 1998

TABLE 5. In this table were combined the data from Sadeghi-Nejad (27), Jorge (28), and Table 1

	Sadeghi-Nejad	Jorge	This study	Total
Population studied (no. of idiopathic Addison)	8	24	14	46
No. of ALD patients identified (%)	5/8 (62)	5/24 (20)	5/14 (35)	15/46 (32)
Age (yr) at onset of Addison[a]				
Mean ± SD	4.5 ± 4.4	10 ± 3.7	20.4 ± 10.1	11.6 ± 9.2
Range	(1–12)	(4–14)	(12–32)	(1–32)
Age (yr) at diagnosis of Addison[a]				
Mean ± SD	7.5 ± 4.8	ND	21.8 ± 11.6	14.6 ± 11.3
Range	(1.5–15)	ND	(12–36)	(1.5–36)
Secondary onset of neurological symptoms[a]	2/5	3/5	3/5	8/15

ND, not determined.
[a] ALD patients.

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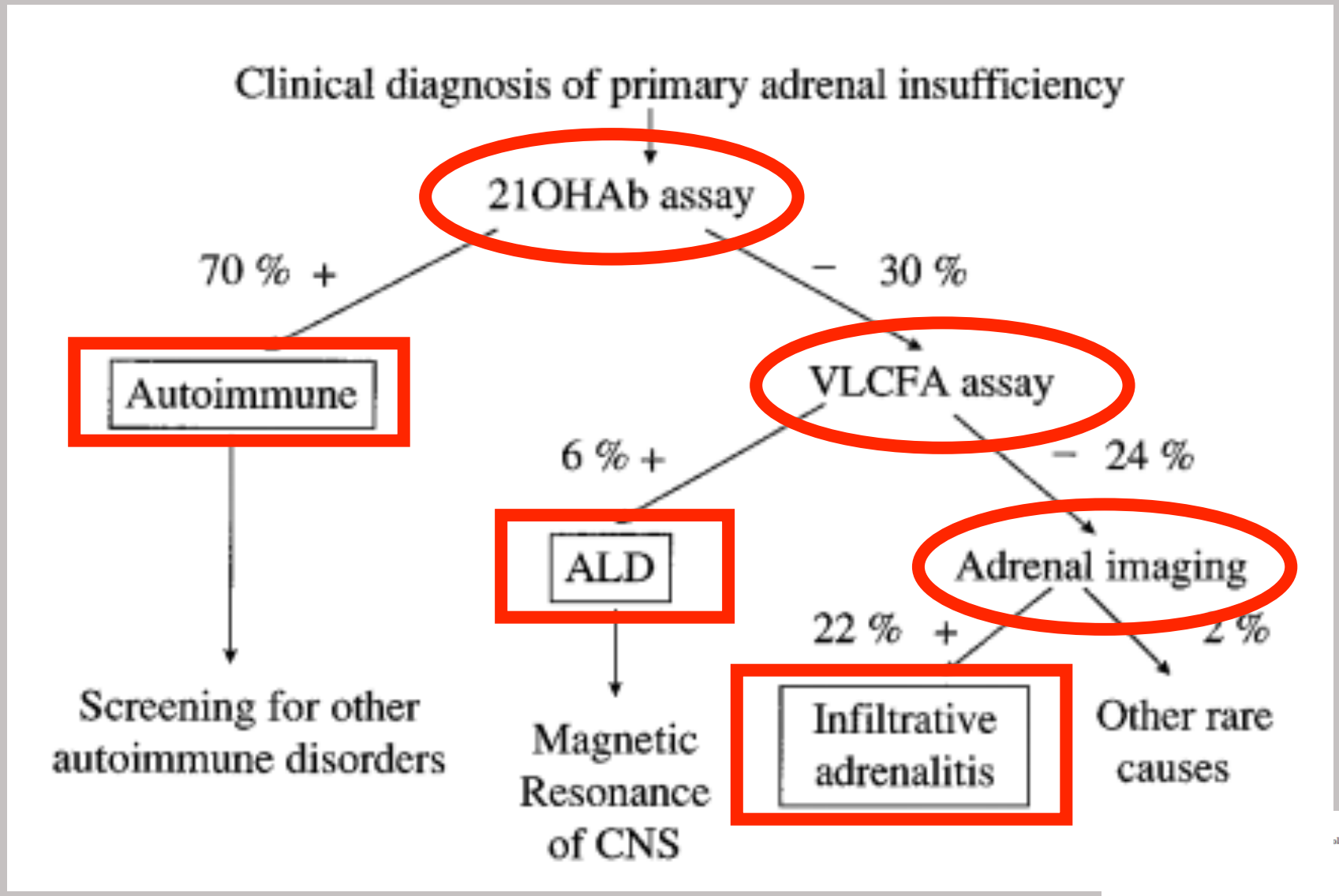
X-Linked Adrenoleukodystrophy Is a Frequent Cause of Idiopathic Addison's Disease in Young Adult Male Patients

STEFANO LAURETI, GIOVANNI CASUCCI, FAUSTO SANTEUSANIO, GABRIELLA ANGELETTI, PATRICK AUBOURG, AND PAOLO BRUNETTI

Department of Internal Medicine and Endocrinological and Metabolic Sciences, University of Perugia (S.L., G.C., F.S., G.A., P.B.), Perugia, Italy; and INSERM U-342, Hôpital Saint Vincent de Paul, Faculté Cochin, Université René Descartes (P.A.), Paris, France



olism

Vol. 83, No. 9
Printed in U.S.A.

Etiological Diagnosis of Primary Adrenal Insufficiency Using an Original Flowchart of Immune and Biochemical Markers*

STEFANO LAURETI, PATRICK AUBOURG, FILIPPO CALCINARO, FRANCIS ROCCHICCIOLI, GIOVANNI CASUCCI, GABRIELLA ANGELETTI, PAOLO BRUNETTI, ÅKE LERNMARK, FAUSTO SANTEUSANIO, AND ALBERTO FALORNI

0021-972X/04/$15.00/0
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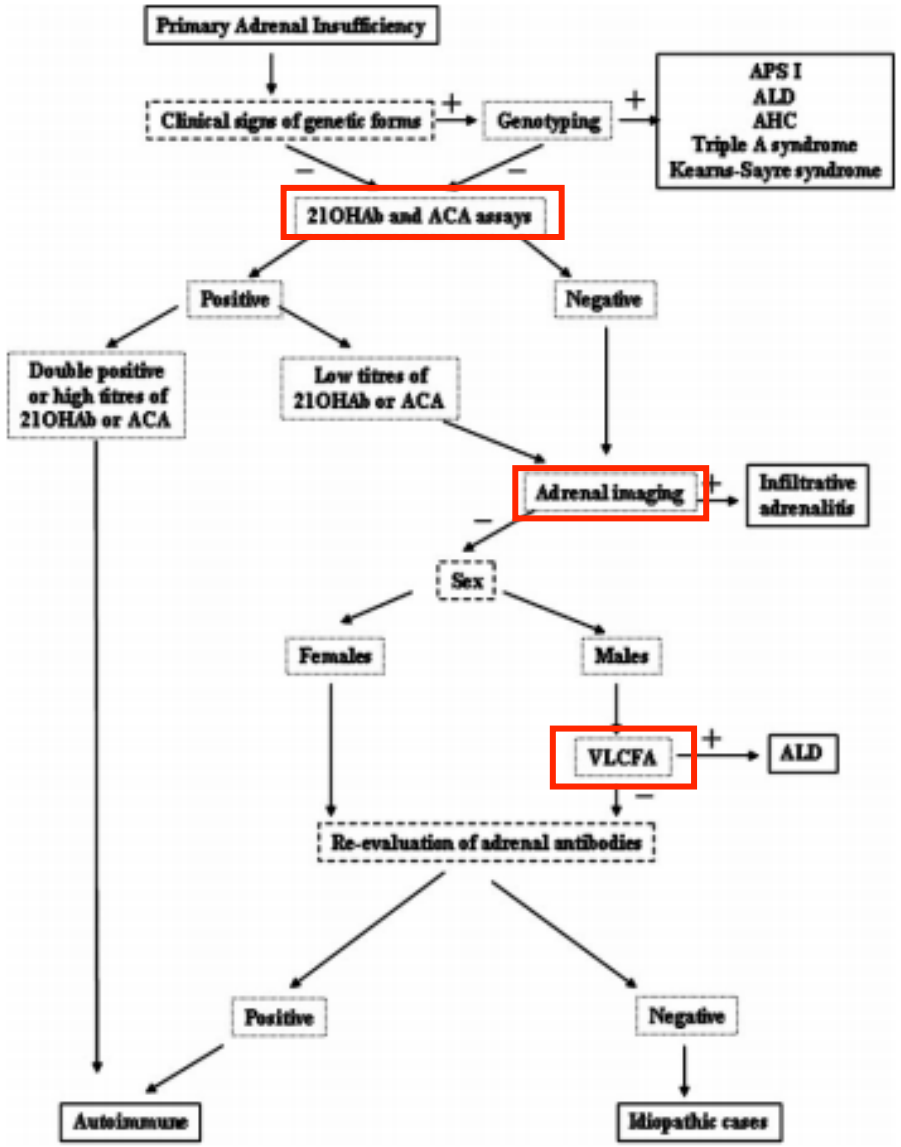
The Journal of Clinical Endocrinology & Metabolism 89(4):1598–1604

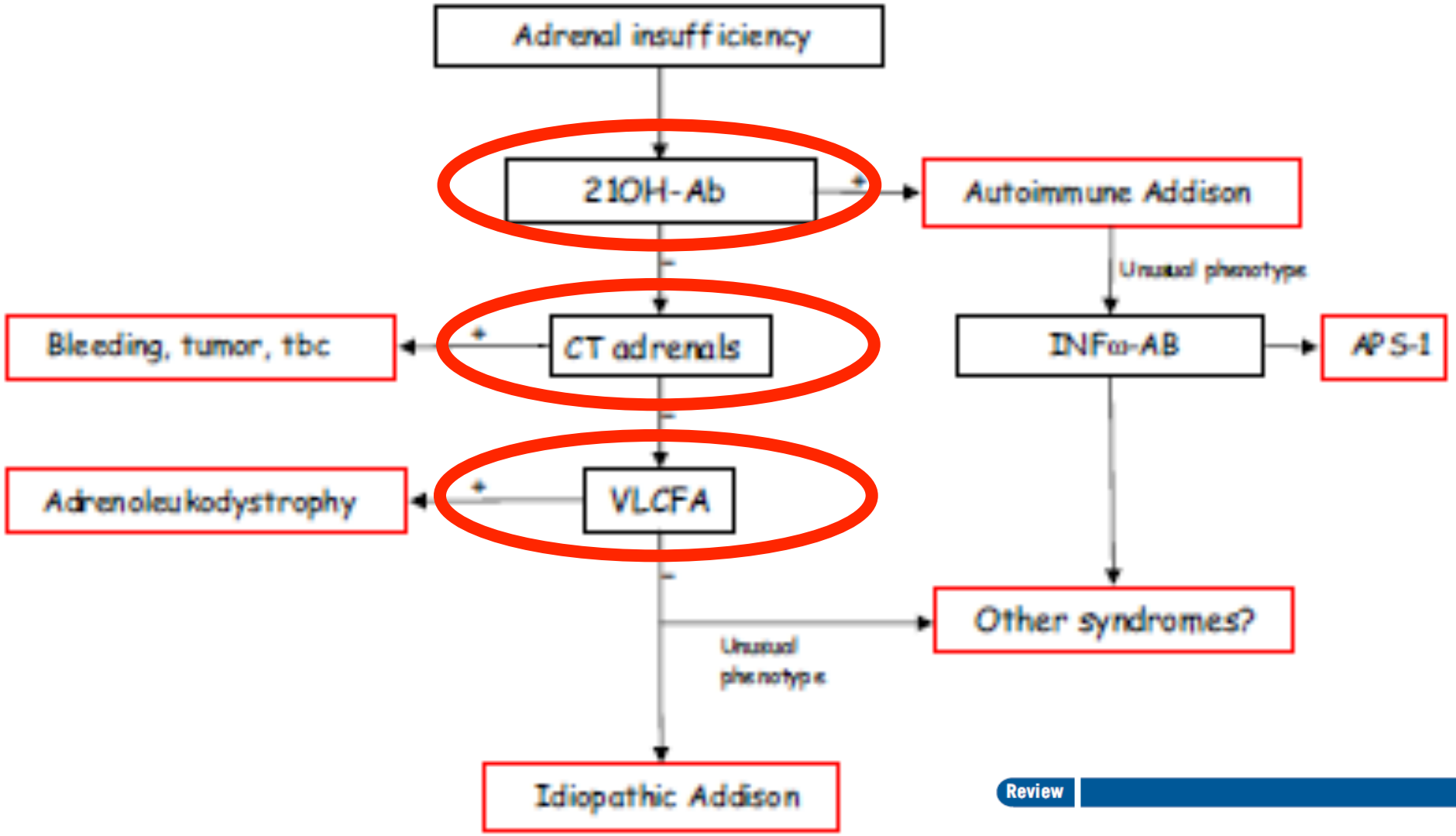
doi: 10.1210/jc.2003-030954

Italian Addison Network Study: Update of Diagnostic Criteria for the Etiological Classification of Primary Adrenal Insufficiency

ALBERTO FALORNI, STEFANO LAURETI, ANNAMARIA DE BELLIS, RENATO ZANCHETTA, CLAUDIO TIBERTI, GIORGIO ARNALDI, VITTORIO BINI, PAOLO BECK-PECCOZ, ANTONIO BIZZARRO, FRANCESCO DOTTA, FRANCO MANTERO, ANTONIO BELLASTELLA, CORRADO BETTERLE, AND FAUSTO SANTEUSANIO ON BEHALF OF THE SIE ADDISON STUDY GROUP

In addition to the authors, the following members of the SIE Addison Study Group contributed to the collection of data and blood samples from patients with primary adrenal insufficiency: B. Ambrosi (Milan), A. Angeli (Turin), E. Arvat (Turin), A. Baccarelli (Milan), L. Barbetta (Milan), M. Boscaro (Ancona), F. Cavagnini (Milan), C. Dal Pra (Padova), E. Ghigo (Turin), R. Giordano (Turin), F. Loré (Siena), M. Mannelli (Florence), G. Mantovani (Milan), P. Paccotti (Turin), F. Pecori-Gilardi (Milan), R. Perniola (Lecce), M. Terzolo (Turin), P. Toja (Milan), M. Torlontano (S. Giovanni Rotondo), V. Toscano (Rome), and V. Trischitta (S. Giovanni Rotondo).





Review
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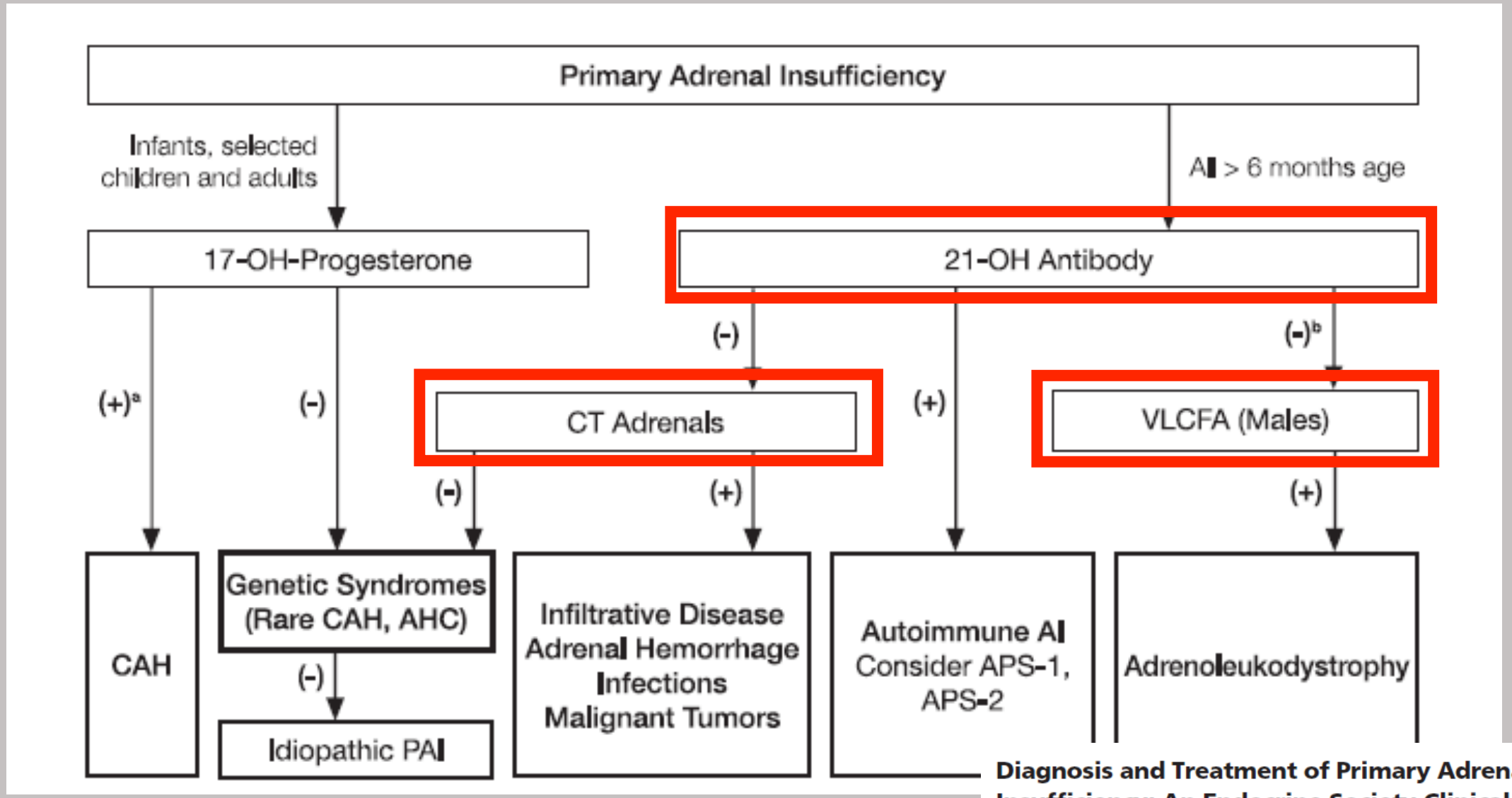

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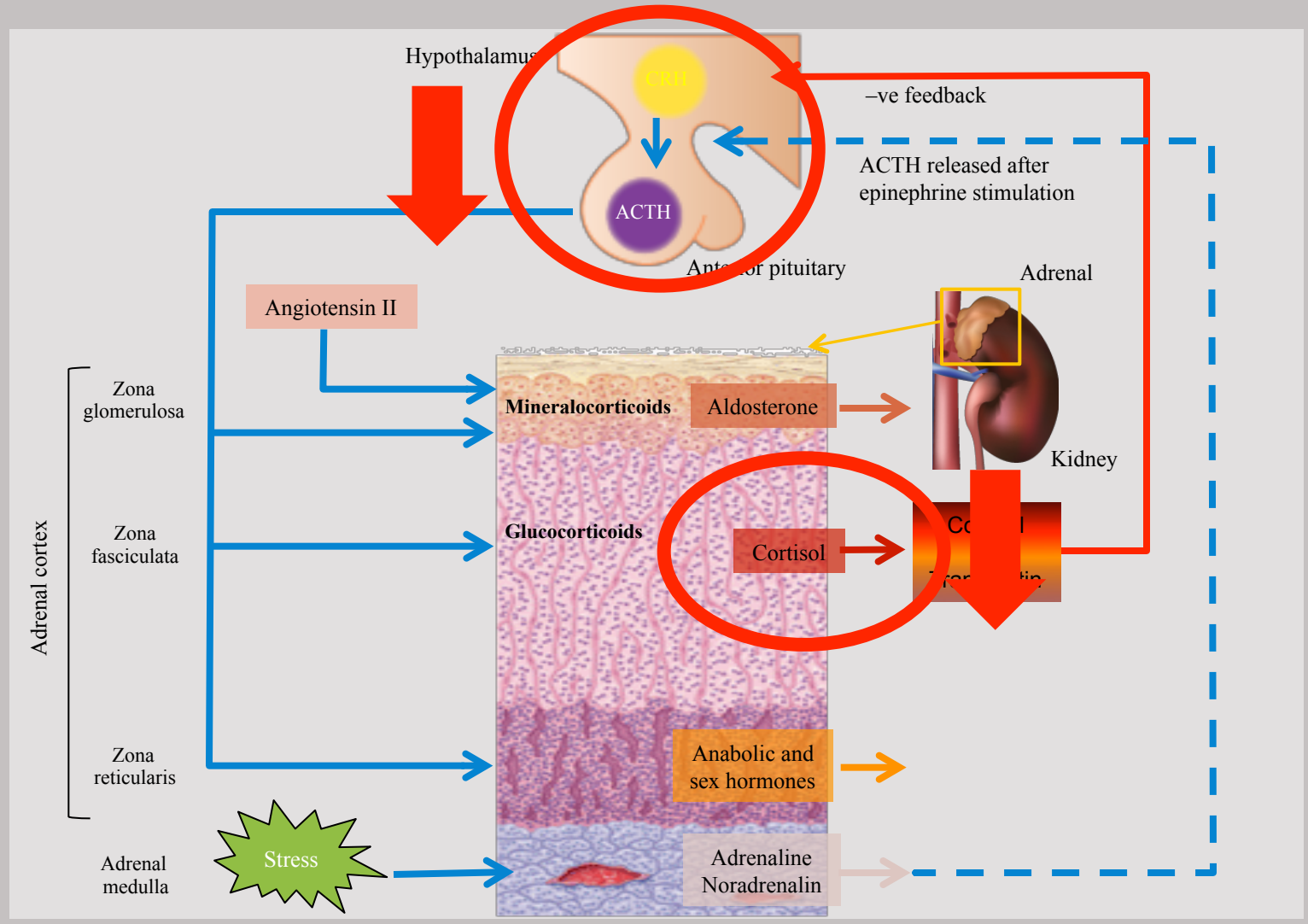
The HPA axis and normal adrenal function



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Iposurrenalismo secondario EPIDEMIOLOGIA

- **Con 150-280 casi per milione è la forma più frequente di iposurrenalismo**
- **Prevalente nelle donne**
- **Picco di età nella sesta decade**

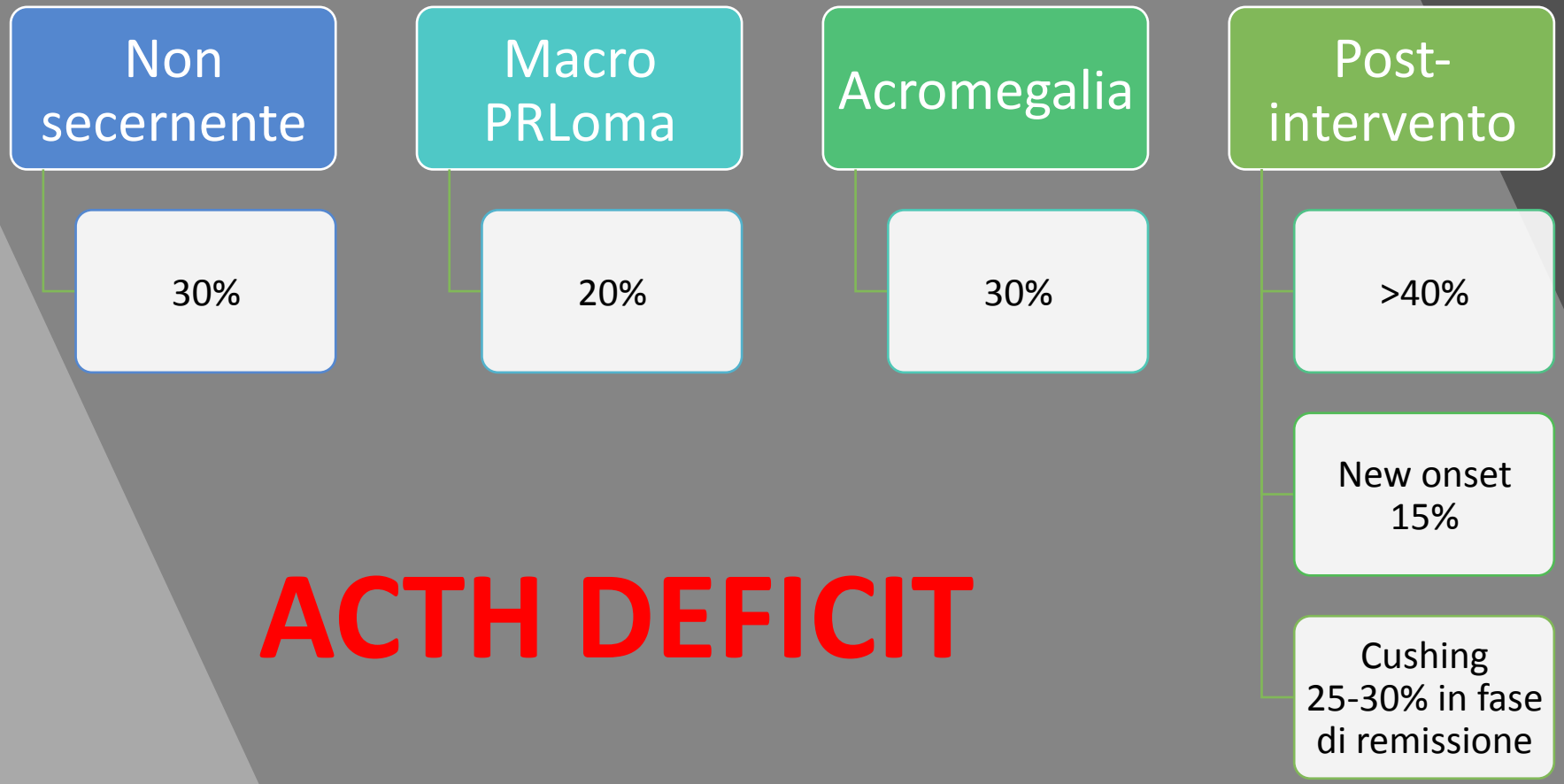
Main causes of secondary adrenal insufficiency[1]

Diagnosis	Pathogenesis
Pituitary tumours	Usually adenomas (rarely carcinoma) Consequence of tumour growth, surgical treatment or both
Other tumours of the hypothalamic-pituitary region	Craniopharyngioma Meningioma Ependymoma Intrasellar or suprasellar metastases
Pituitary irradiation	Craniospinal irradiation in leukaemia Radiation for tumours outside the HPA axis Irradiation of pituitary tumours
Lymphocytic hypophysitis	May be isolated or associated with APS
Isolated congenital ACTH deficiency	Pro-opiomelanocorticotrophic cleavage defect?

APS: autoimmune polyendocrine syndrome

1. Arlt W and Allolio B. Lancet 2003;361:1881–1893

Una causa, una probabilità



ACTH DEFICIT

MALATTIE IPOFISARIE
Lesioni espansive: Adenomi; Cisti; Altri tumori benigni
Neurochirurgia dell'ipofisi
Radiazioni
Lesioni infiltrative: Ipofisiti; Emocromatosi
Sindrome di Sheehan
Apoplessia ipofisaria
Malattie Genetiche: Pit-1 mutazione

MALATTIE IPOTALAMICHE
Lesioni espansive benigne e maligne: Craniofaringioma; Metastasi (polmone, stomaco, ecc)
Processi infiltrativi: sarcoidosi ; Istiocitosi a cellule di Langerans
Radiazioni: ETP SNC / Naso-faringe
Traumi (fratture della base)
Infezioni: Meningite TBC

DEFICIT DI ACTH

• MENINGITI	30%
• EMORRAGIA SUB-ARACNOIDEA	16%
• TRAUMA CRANICO	11%
• RADIAZIONI ipotalamo-ipofisi (tradizionale)	60-80%
• RADIAZIONI ipotalamo-ipofisi (gamma-knife)	10-15%
• RADIAZIONI cranio (per tumori non ipofisari)	25%

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LE DISFUNZIONI ENDOCRINE DA FARMACI INIBITORI DEI *CHECKPOINT* IMMUNITARI

Responsabile Editoriale
Renato Cozzi

Vincenzo Di Donna (dottdido@libero.it) **& Salvatore Maria Corsello**
UO di Endocrinologia, Università Cattolica del Sacro Cuore, Policlinico "A. Gemelli", Roma

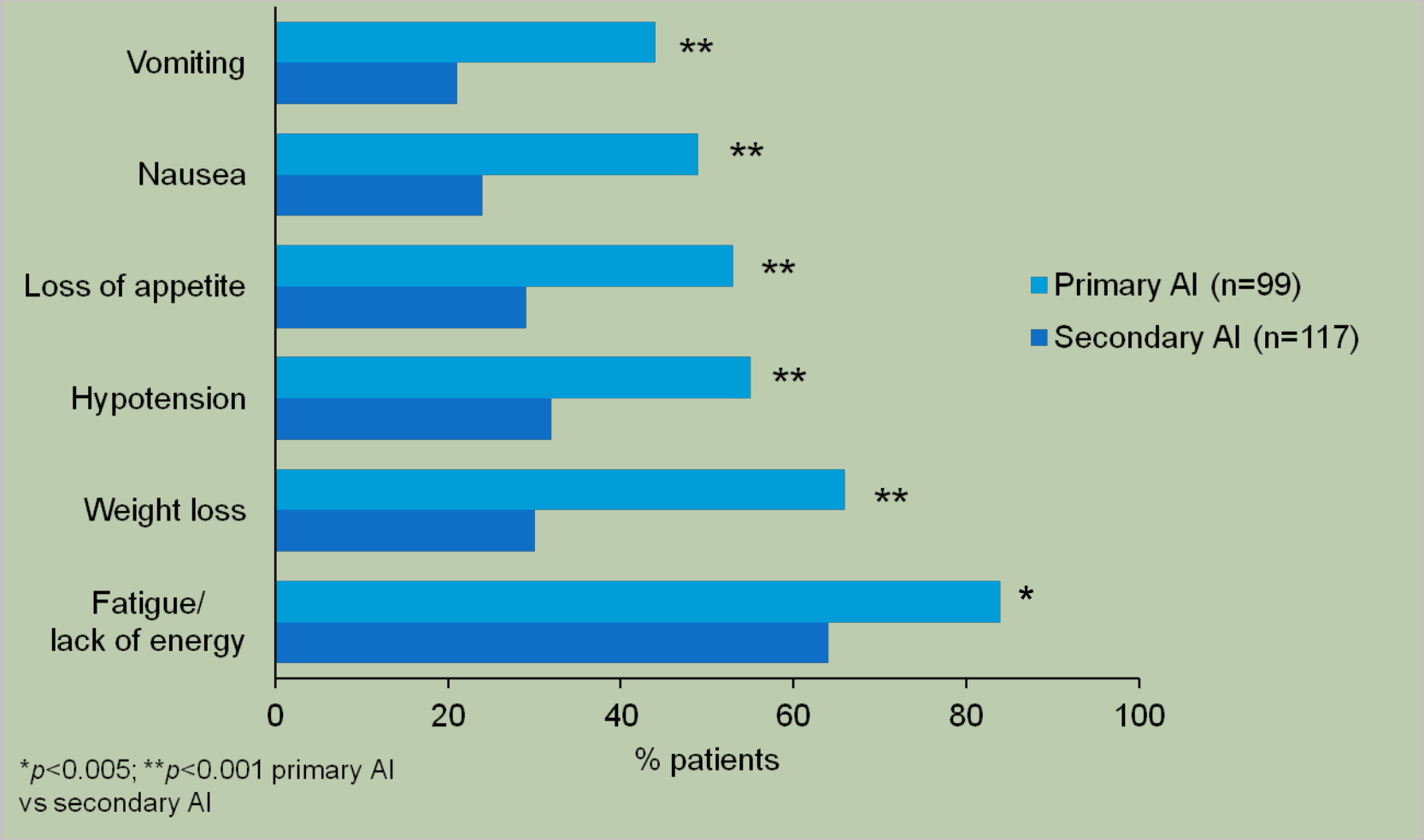
- Sono oggi disponibili anticorpi monoclonali anti-CTLA-4, anti-PD-1 e anti-PD-1 ligando per la terapia di pazienti affetti da melanoma e la maggior parte dei tumori solidi (in particolare cancro polmonare e renale). Tra le molecole approvate per la pratica clinica, ci sono ipilimumab e, più recentemente, pembrolizumab e nivolumab.
- L'**epoca di insorgenza degli effetti collaterali endocrini è di circa 9 settimane** (*range* 5-36) dopo l'inizio della terapia, ma sono possibili anche manifestazioni più precoci o tardive.
- In particolare, l'incidenza di ipofisite varia da 0 a 17% per ipilimumab, da 0.4 a 5% per tremelimumab ed è < 1% per nivolumab e pembrolizumab. In una recente metanalisi sull'argomento, Abdel-Rahaman e coll hanno riportato un **rischio relativo cumulativo** di ipofisite di **22.03** (IC95% 5.52-56.94, p < 0.00001).

- ipotiroidismo centrale: ~ 87%;
- ipogonadismo ipogonadotropo: ~ 85%;
- iposurrenalismo secondario: ~ 73%;
- deficit di GH: ~ 25%;
- ipo- (più spesso) o iperprolattinemia: ~ 25%.

In circa la metà dei casi, le disfunzioni tiroidea e gonadica possono essere reversibili, con una mediana di 10 e 13 settimane rispettivamente in uno studio, mentre l'iposurrenalismo è quasi sempre permanente, in maniera purtroppo non prevedibile.

STADIAZIONE PRE-TRATTAMENTO / MANAGEMENT IN CORSO DI TRATTAMENTO

Frequency of most common symptoms in primary and secondary adrenal insufficiency[1]



Results from a questionnaire survey of 216 patients with primary (46%) or secondary (54%) AI conducted in Germany. Data are symptoms at time of diagnosis.

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

CENTRAL ADRENAL INSUFFICIENCY

1.0 Diagnosis of hypopituitarism

Central adrenal insufficiency

1.1 We suggest measuring serum cortisol levels at 8–9 AM as the first-line test for diagnosing central adrenal insufficiency (AI). (2⊕◯◯◯)

1.2 We recommend against using a random cortisol level to diagnose AI. (1⊕⊕◯◯)

1.3 We suggest that a cortisol level <3 μg/dL is indicative of AI and a cortisol level >15 μg/dL likely excludes an AI diagnosis. (2⊕◯◯◯)

- 1.4 We suggest performing a corticotropin stimulation test when morning cortisol values are between 3 and 15 g/dL to diagnose AI. Peak cortisol levels <18.1 mcg/dL (500 nmol/L) at 30 or 60 minutes indicate AI. (2⊗⊗◯◯)
- 1.5 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. (2⊗⊗◯◯)

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

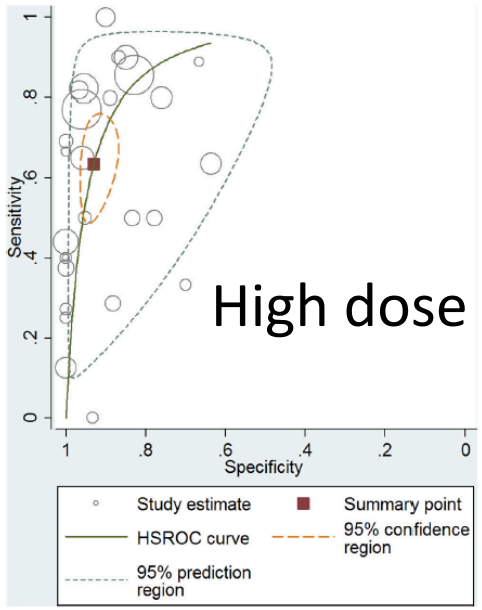
J Clin Endocrinol Metab, February 2016, 101(2):427–434

Table 1. Meta-Analysis Results: ACTH Stimulation Tests for the Diagnosis of Secondary Adrenal Insufficiency

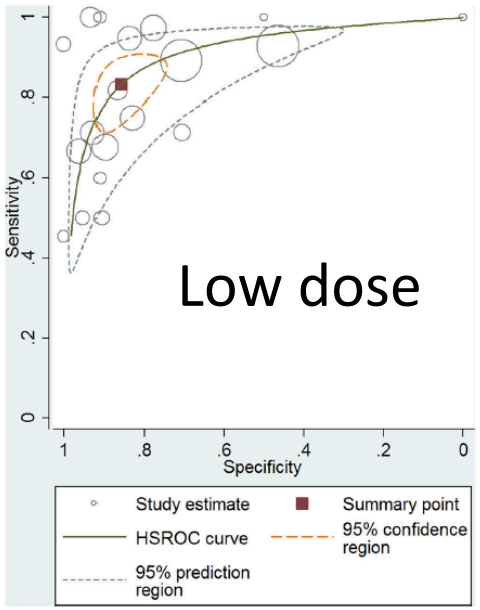
	Estimate	95% CI
Adult High-Dose ACTH Stimulation Test		
Sensitivity	0.64	0.52–0.73
Specificity	0.93	0.89–0.96
Likelihood ratio for positive test	9.1	5.7–14.6
Likelihood ratio for negative test	0.39	0.30–0.52
Diagnostic odds ratio	23	13–42
Adult Low-Dose ACTH Stimulation Test		
Sensitivity	0.83	0.75–0.89
Specificity	0.86	0.78–0.91
Likelihood ratio for positive test	5.9	3.8–8.9
Likelihood ratio for negative test	0.19	0.13–0.29
Diagnostic odds ratio	30	18–50
Children High-Dose ACTH Stimulation Test		
Sensitivity	0.36	0.10–0.73
Specificity	0.99	0.81–0.99
Likelihood ratio for positive test	43.5	1–1891.2
Likelihood ratio for negative test	0.65	0.36–1.15
Diagnostic odds ratio	67	1–4152
Children Low-Dose ACTH Stimulation Test		
Sensitivity	0.69	0.28–0.93
Specificity	0.91	0.63–0.98
Likelihood ratio for positive test	7.7	1.3–44.8
Likelihood ratio for negative test	0.34	0.10–1.18
Diagnostic odds ratio	23	2–313

Table 2. ACTH Stimulation Tests for the Diagnosis of Secondary Adrenal Insufficiency Based on Cortisol Cutoff

Cortisol Cutoff (nmol/liter)	LR+	LR−	Diagnostic OR	No. of Studies	LR+	LR−	Diagnostic OR	No. r of Studies	*P* Value (for Difference)
Adults									
	High-Dose ACTH Test				**Low-Dose ACTH Test**				
500–30 minutes	6.3 (2.5–16)	0.32 (0.20–0.51)	20 (5–75)	6	NR	NR	NR	NR	NA
500–peak	12.4 (6.7–23.0)	0.48 (0.32–0.72)	26 (11–60)	14	7.1 (4.3–11.6)	0.21 (0.13–0.33)	34 (17–68)	11	.631
550–peak	6.4 (3.4–12)	0.36 (0.21–0.61)	18 (8–43)	8	3.8 (1.5–9.4)	0.23 (0.11–0.49)	16 (6–40)	6	.855
Children									
	High-Dose ACTH Test				**Low-Dose ACTH Test**				
500–peak	15.96 (2.12–120.04)	0.37 (0.01–12.95)	40.67 (1.1–1424.1)	2	18.3 (2.04–164.73)	0.31 (0.5–1.9)	93.63 (14.6–620.1)	3	.686
550–peak	6.1 (1.09–34.17)	0.78 (0.58–1.06)	7.96 (1.2–51.4)	2	4.3 (2.65–7.06)	0.2 (0.02–1.92)	24.8 (1.73–356.9)	2	.494



High dose



Low dose

Initial diagnostic work-up in adults with suspected adrenal insufficiency

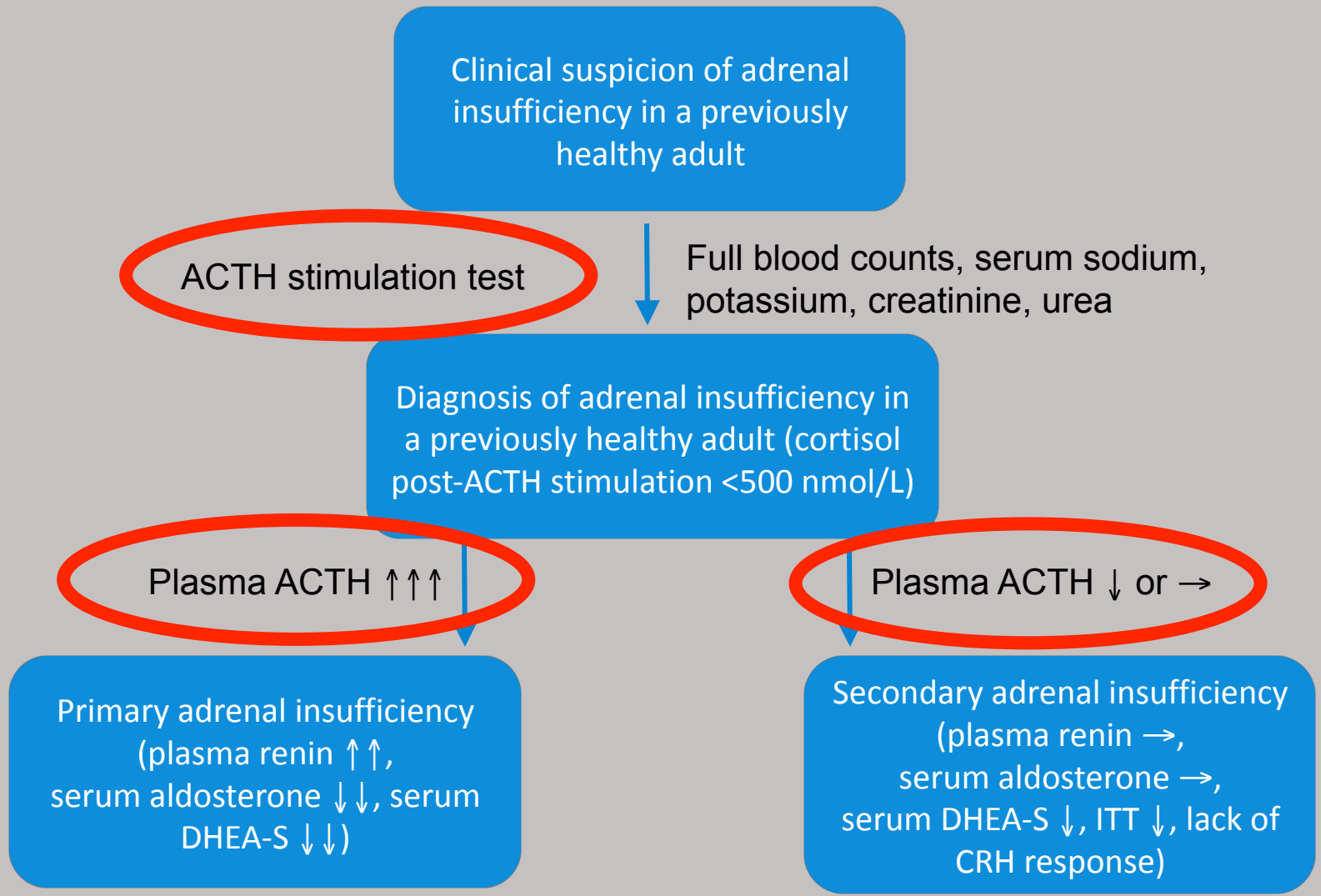


Figure adapted from Arlt

Arlt W. J Clin Endocrinol Metab 2009;94:1059–1067

Establishing the cause of adrenal insufficiency

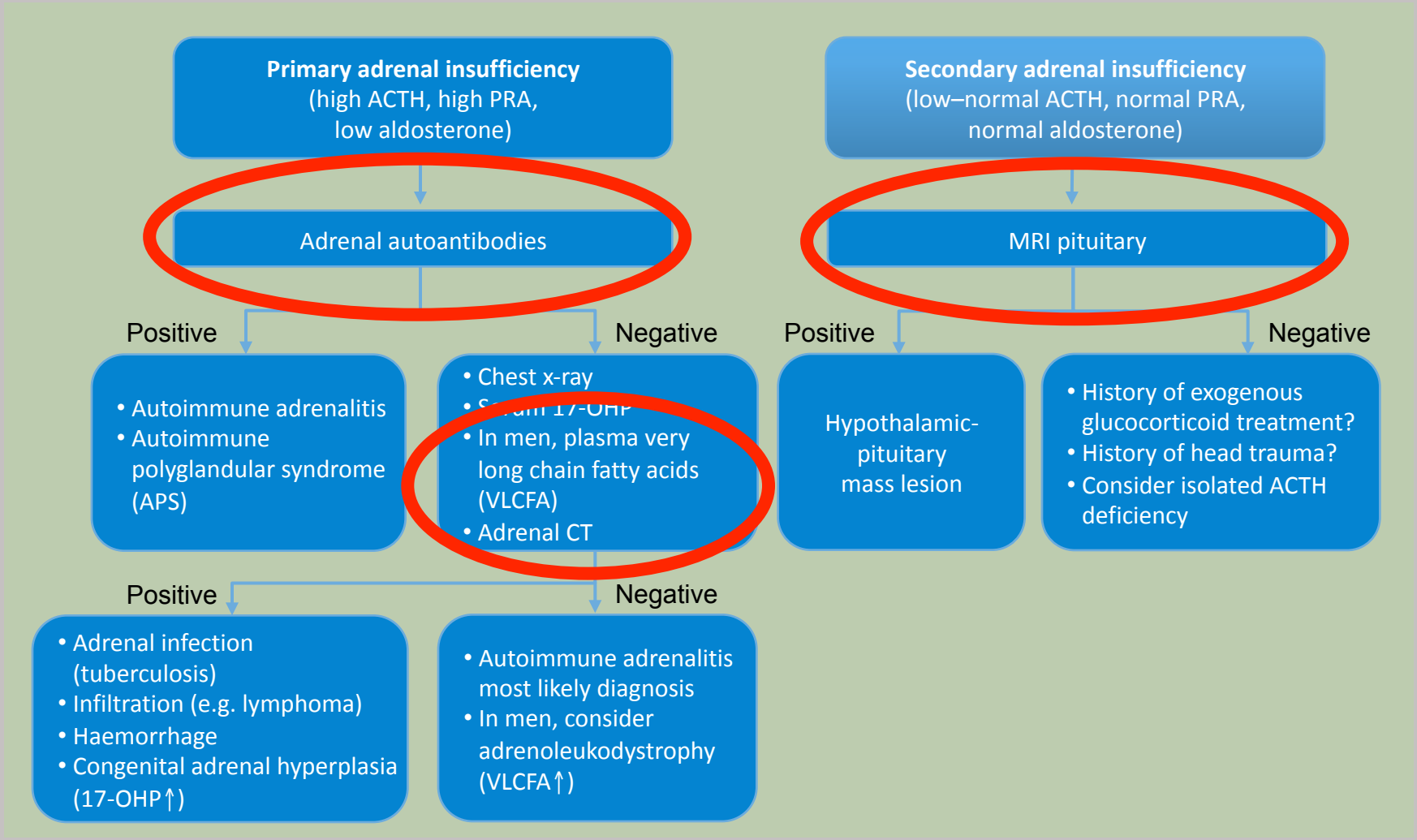


Figure adapted from Arlt

Arlt W. In: Longo DL et al (editors). Harrison's Principles of Internal Medicine, 18th ed. 2011. pp 2940–2961