CRITICAL REVIEW OF THE ENDOCRINE SOCIETY GUIDELINE ON ADRENAL INSUFFICIENCY

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Bornstein,R., et al. J Clin Endoctinol Metab, February 2016, 101(2):364-389

LEARNING OBJECTIVES

- Diagnose AI and generate an appropriate differential diagnosis

Recognize other autoimmune conditions that may be coincident with adrenal failure.

Develop a long-term treatment plan that will prevent adrenal crises and minimize untoward effects of GC and MC replacement.

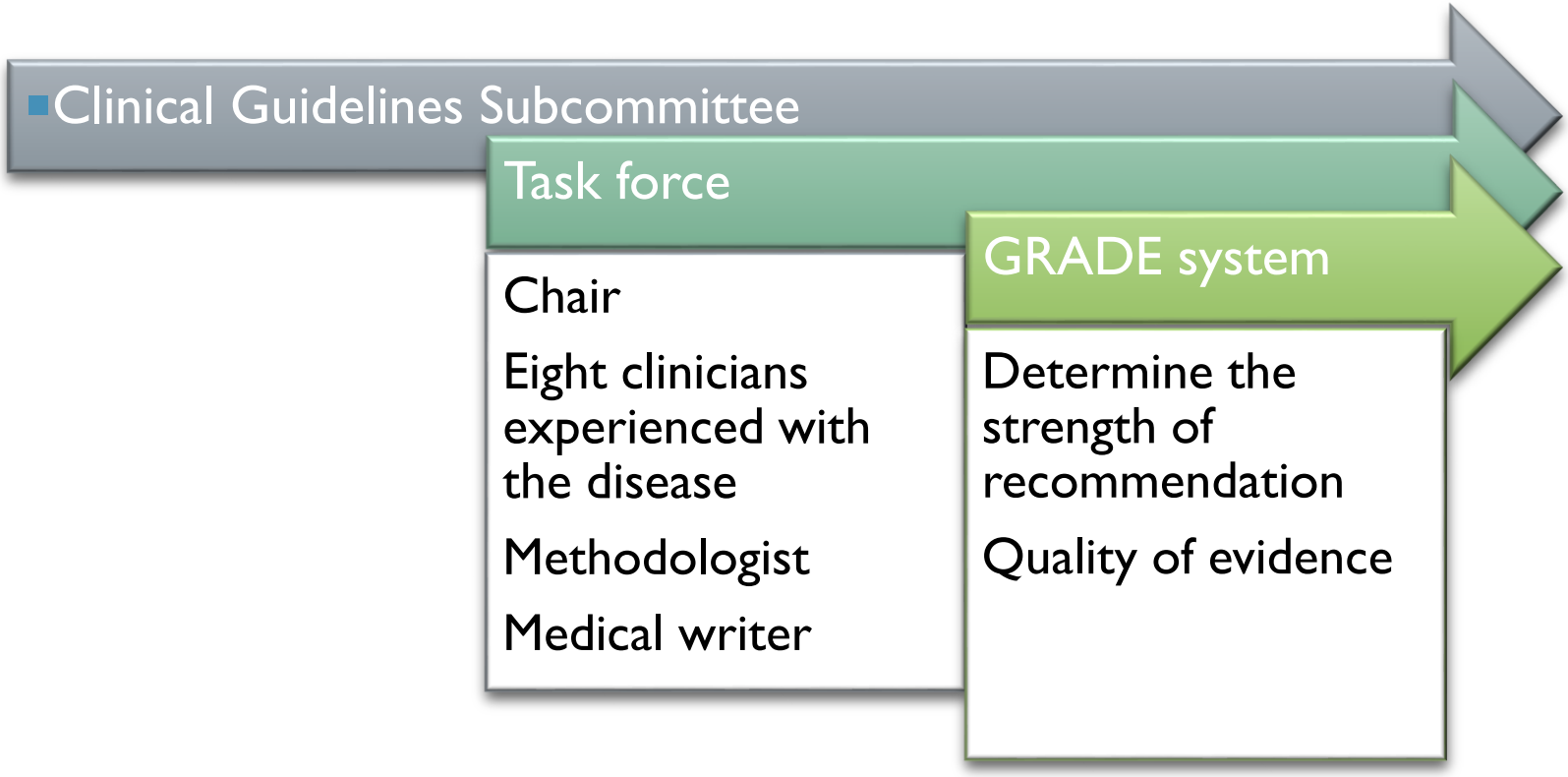
BARRIERS TO OPTIMAL PRACTICE

- Physiological replacement therapy is not available.

Modalities for early intervention in autoimmune Addison's disease are missing.

International guidelines have only recently been published and the best treatment and diagnostic options might not be widely available.

METHOD OF DEVELOPMENT OF EVIDENCE-BASED CLINICAL PRACTICE GUIDELINES



GRADE SYSTEM

Strong recommendation	• "We Recommend" and the number 1
Weak recommendation	• "We suggest" and the number 2
Quality of evidence	• ⊕OOO- very low quality evidence • ⊕⊕OO- low quality evidence • ⊕⊕⊕O- moderate quality evidence • ⊕⊕⊕⊕- high quality evidence
Remarks	• Considered suggestions

COMMISSIONED SYSTEMATIC REVIEWS

First Systematic Review

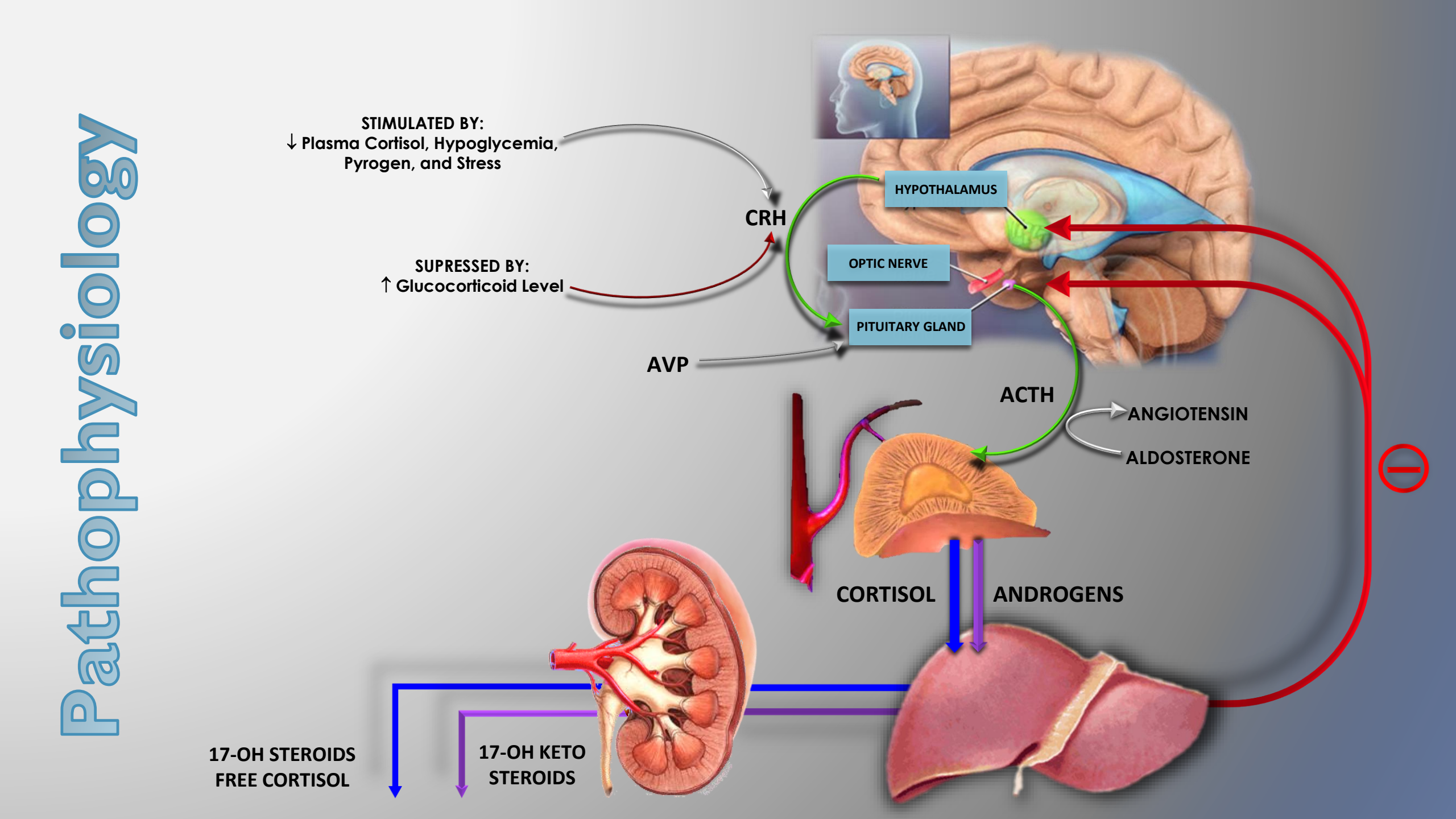
- Comparison of the diagnostic accuracy of high-dose ACTH vs low-dose ACTH stimulation tests for the initial dx.
- Five studies evaluated the dx accuracy of the high-dose ACTH stimulation test and none for the low-dose.
- The sensitivity of the high-dose ACTH stimulation test for the dx of PAI was 92% (95% confidence interval, 81–97%).

COMMISSIONED SYSTEMATIC REVIEWS (CONT.)

Second Systematic Review

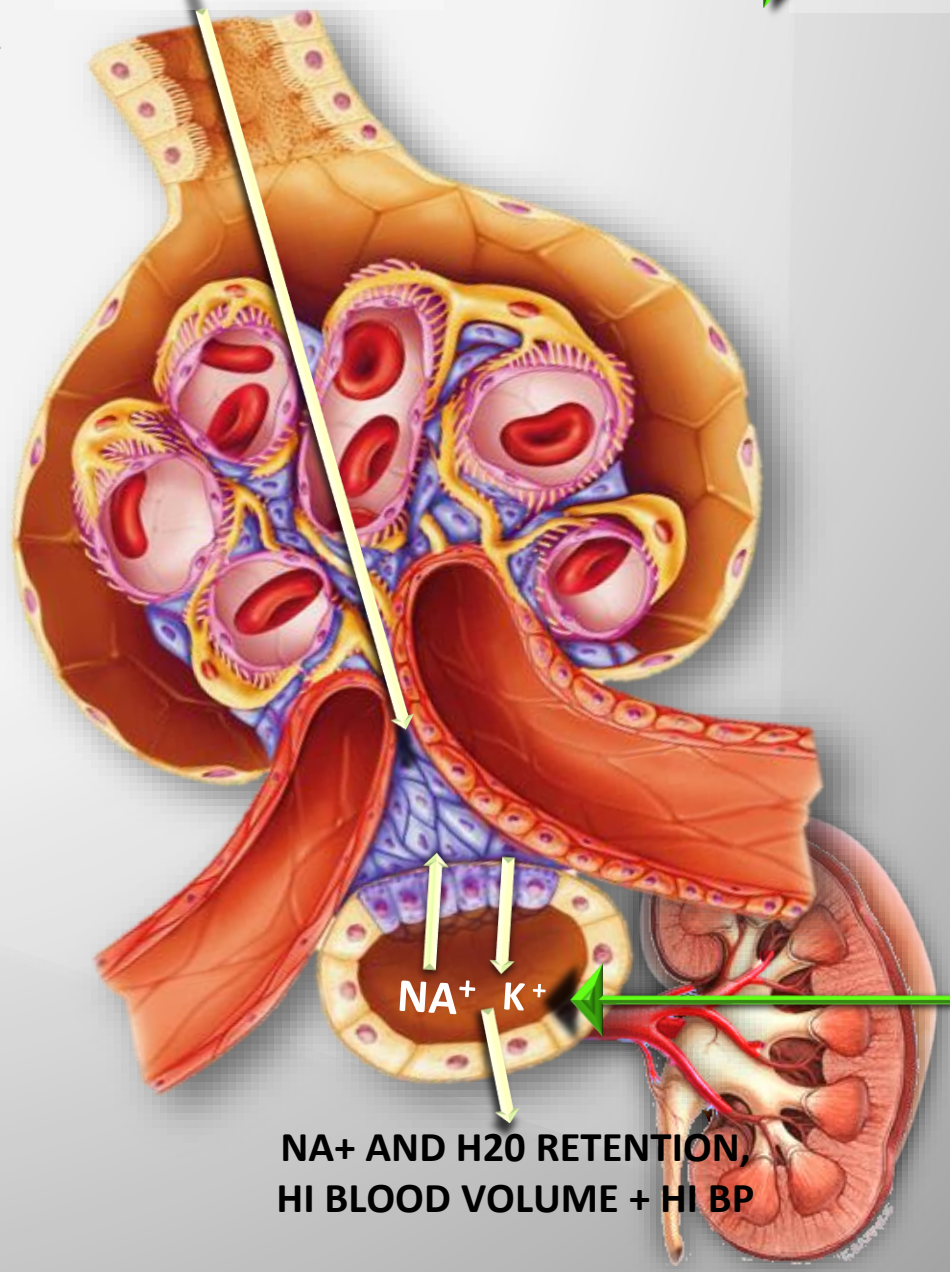
- Comparison of various glucocorticoid replacement regimens.
- 15 relevant observational studies.
- Poor quality data on mortality, bone density, and incidence of adrenal crisis.
- HRQoL- no statistically significant difference with dosages equal to or higher than 30mg/d of hydrocortisone vs regimens with dosages less than 30/mg/d.
- Very low quality evidence suggests that ER or dual-release forms of GC may have higher HRQoL scores.

Pathophysiology



ANGIOTENSINOGEN
α -2-GLOBULIN
FROM LIVER

RENIN FROM JGA → ANGIOTENSINOGEN → CONVERTING ENZYME IN LUNG → ANGIOTENSINOGEN II → ALDOSTERONE

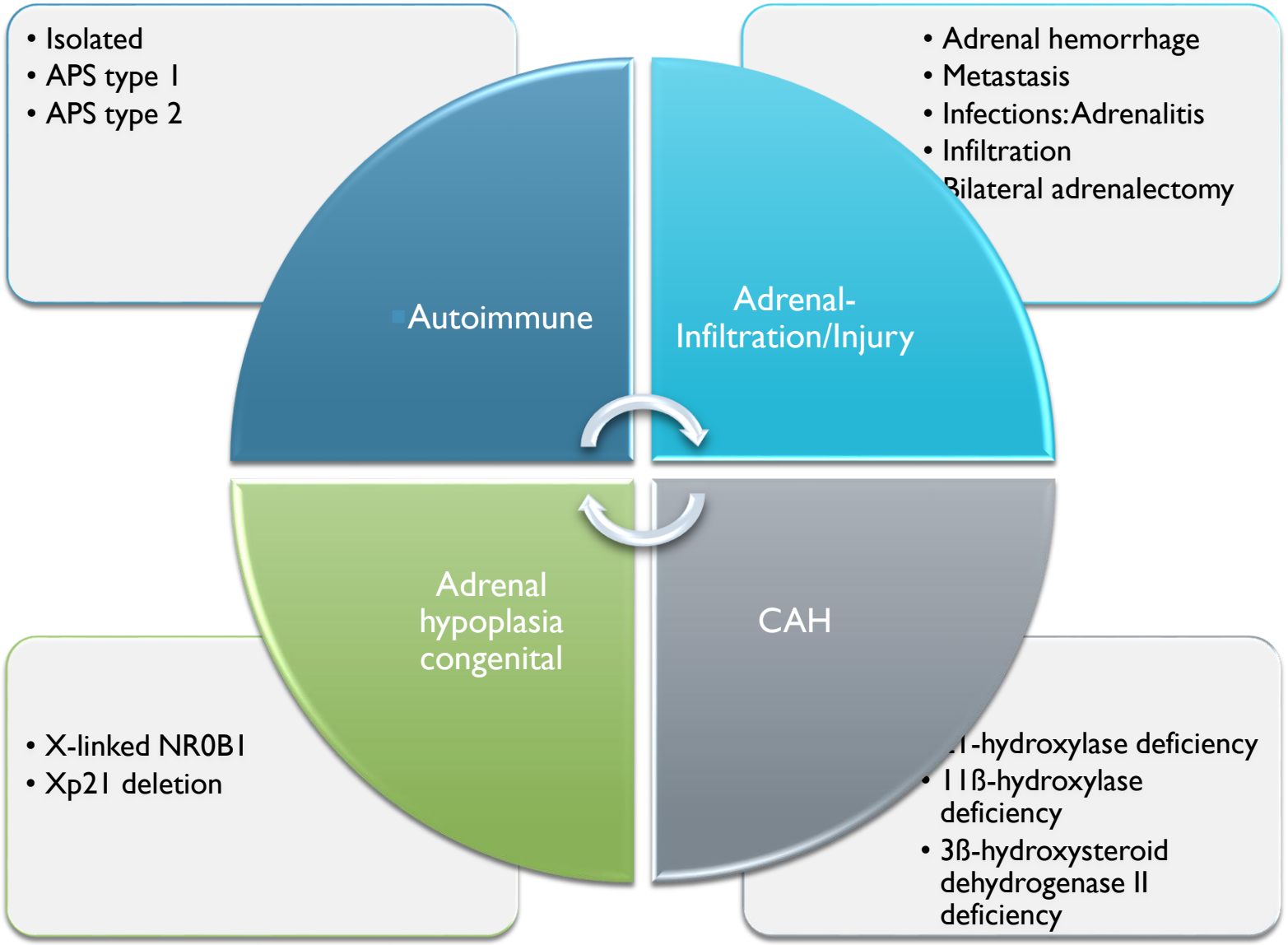


NA+ AND H20 RETENTION,
HI BLOOD VOLUME + HI BP

Pathophysiology

Clinical Features of Adrenal Insufficiency and Adrenal Crisis		
Symptoms	Signs	Routine laboratory tests
Adrenal Insufficiency		
Fatigue	Hyperpigmentation (primary only), particularly of sun-exposed areas, skin creases, mucosal membranes, scars, areola of breast	Hyponatremia
Weight loss	Low blood pressure with increased postural drop	Hyperkalemia
Postural dizziness	Failure to thrive in children	Uncommon: hypoglycemia, hypercalcemia
Anorexia, abdominal discomfort		
Adrenal Crisis		
Severe weakness		Hyponatremia
Syncope	Hypotension	Hyperkalemia
Abdominal pain, nausea, vomiting; may mimic acute abd pain	Abdominal tenderness/guarding	Hypoglycemia
Back pain	Reduced consciousness, delirium	Hypercalcemia
Confusion		

Major Etiologies of PAI



Major etiologies of PAI

ACTH insensitivity syndromes

- Type 1
- Type 2
- Familial glucocorticoid deficiency
- Allgrove's syndrome

Drug induced

- Adrenal enzyme inhibitors: mitotane, ketoconazole, metyrapone, etomidate
- Drugs that accelerate cortisol metabolism
- T4
- CTLA-inhibitors

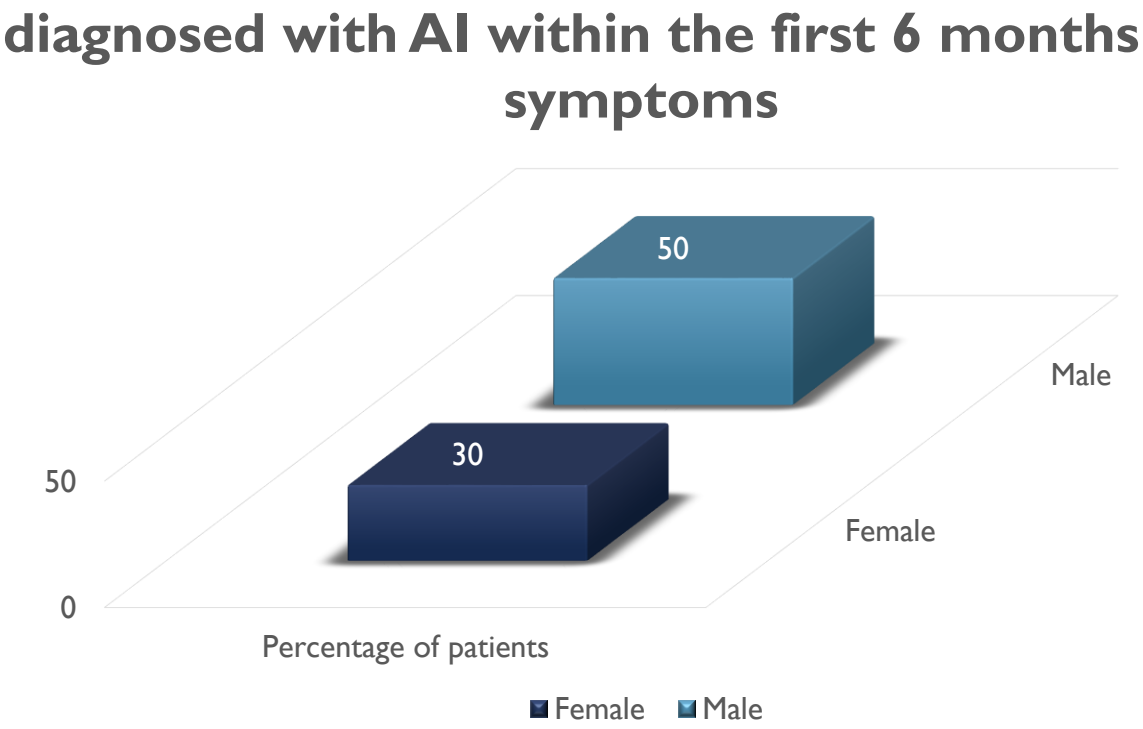
Other metabolic disorders

- Mitochondrial disease
- Adrenoleukodystrophy
- Wolman's disease

1. WHO SHOULD BE TESTED AND HOW?

- 1.1 We recommend diagnostic testing to exclude PAI in acutely ill patients with otherwise unexplained symptoms or signs suggestive of PAI. (1 ⊕⊕⊕O
- 1.2 We recommend confirmatory testing with the corticotropin stimulation test in patients with clinical symptoms or signs suggesting PAI when the patient's condition and circumstance allow.
- 1.3 In patients with severe adrenal insufficiency symptoms or adrenal crisis, we recommend immediate therapy with iv hydrocortisone at an appropriate stress dose prior to the availability of the results of diagnostic tests.

DELAYED DIAGNOSIS OF ADRENAL INSUFFICIENCY IS COMMON: A CROSS-SECTIONAL STUDY IN 216 PATIENTS



20% of patients had symptoms for >5 years before dx

>67% of patients consulted at least 3 physicians

BLEICKEN B, ET AL. *AM J MED SCI*. 2010;339:525–531.

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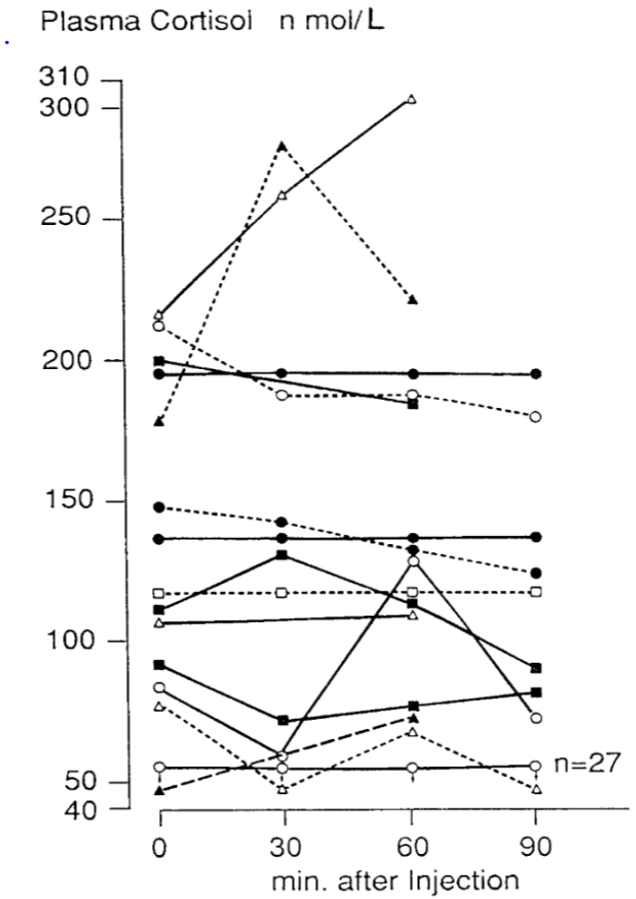
RAPID ACTH TEST IN 41 PATIENTS WITH PAI



- In 27 patients (o with arrows), all measurements were less than 55 nmol/L. Other symbols and lines represent single patients with detectable cortisol levels.

ACTH-(I-24) (250 mcg) was injected IM immediately after the basal blood sample was taken (0 min).

OELKERS W, DIEDERICH S, BÄHR V. DIAGNOSIS AND THERAPY SURVEILLANCE IN ADDISON'S DISEASE: RAPID ADRENOCORTICOTROPIN (ACTH)TEST AND MEASUREMENT OF PLASMA ACTH, RENIN ACTIVITY, AND ALDOSTERONE. J CLIN ENDOCRINOL METAB. 1992;75:259–264.

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2.0 OPTIMAL DIAGNOSTIC TESTS

- 2.1We suggest the standard dose (250 mcg for adults and children ≥ 2y of age,15 mcg/kg for infants, and 125 mcg 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 mcg/dL) (assay dependent) at 30 or 60 minutes indicate adrenal insufficiency. 2⊕⊕○○

META-ANALYSIS RESULTS ON COSYNTROPIN STIMULATION TEST FOR PAI DIAGNOSIS

Table 1. The 250-μg Cosyntropin Stimulation Test in Patients with Primary Adrenal Insufficiency*

Study (Reference)†	Cosyntropin Route and Time after Injection‡	Serum Cortisol Cutoff Level	Sensitivity§	Specificity§	Positive Likelihood Ratio‖	Negative Likelihood Ratio‖
	min	*nmol/L*	*% (n/n)*			
Speckart et al. (27)	IV, 60	415	100 (6/6)	100 (9/9)	>100	0
Nelson and Tindall (14)	IV, 60	415	100 (7/7)	100 (69/69)	>100	0
Oelkers et al. (28)	IM, 60	415	100 (41/41)	–	–	–
Fiad et al. (29)	IV, 60	415	100 (12/12)	100 (55/55)	>100	0
Kong and Jeffcoate (23)	IV, 60	415	75 (6/8)	–	–	–
Gonzalez-Gonzalez et al. (20)	IV, 60	415	82 (9/11)	100 (46/46)	>100	0.18
Soule (30)	IV, 60	415	95 (35/37)	–	–	–
Speckart et al. (27)	IV, 30	415	100 (6/6)	88 (7/8)	8.3	0
Dluhy et al. (13)	IM, 30	415	100 (5/5)	100 (12/12)	>100	0
Oelkers et al. (28)	IM, 30	415	100 (41/41)	–	–	–
Kong and Jeffcoate (23)	IV, 30	415	89 (16/18)	–	–	–
Gonzalez-Gonzalez et al. (20)	IV, 30	415	82 (9/11)	100 (46/46)	>100	0.18

DORIN RI, QUALLS CR, CRAPO LM. DIAGNOSIS OF ADRENAL INSUFFICIENCY. ANN INTERN MED. 2003;139:194-204.

Geometric Mean of Post-ACTH Stimulation Cortisol Concentrations in Males, Non-OCP Female And OCP-female Subjects

Assay	Males $n = 60$	Non-OCP females $n = 79$	P-value*	OCP females $n = 24$	P-value†
GC-MS	563 (418–757)	555 (421–731)	0·594	870 (643–1177)	<0·001
Centaur	599 (448–802)‡	578 (446–750)‡	0·138	763 (619–940)	<0·001
Architect	577 (430–773)‡	542 (416–707)‡	0·012	747 (577–967)	<0·001
E170	772 (574–1039)‡	712 (524–967)‡	0·003	1026 (791–1330)	<0·001
Immulite (2000)	641 (469–874)‡	628 (478–826)‡	0·449	850 (688–1051)	<0·001
Access	625 (459–852)‡	594 (455–777)‡	0·045	757 (604–948)	<0·001

Results are expressed as geometric mean (2·5th–97·5th percentile) in nM.
*P-value for difference between genders.
†P-value for difference between women taking an oral contraceptive pill and those who were not.
‡P-value for immunoassay *vs* gas chromatography-mass spectrometry (GC-MS) < 0·02.

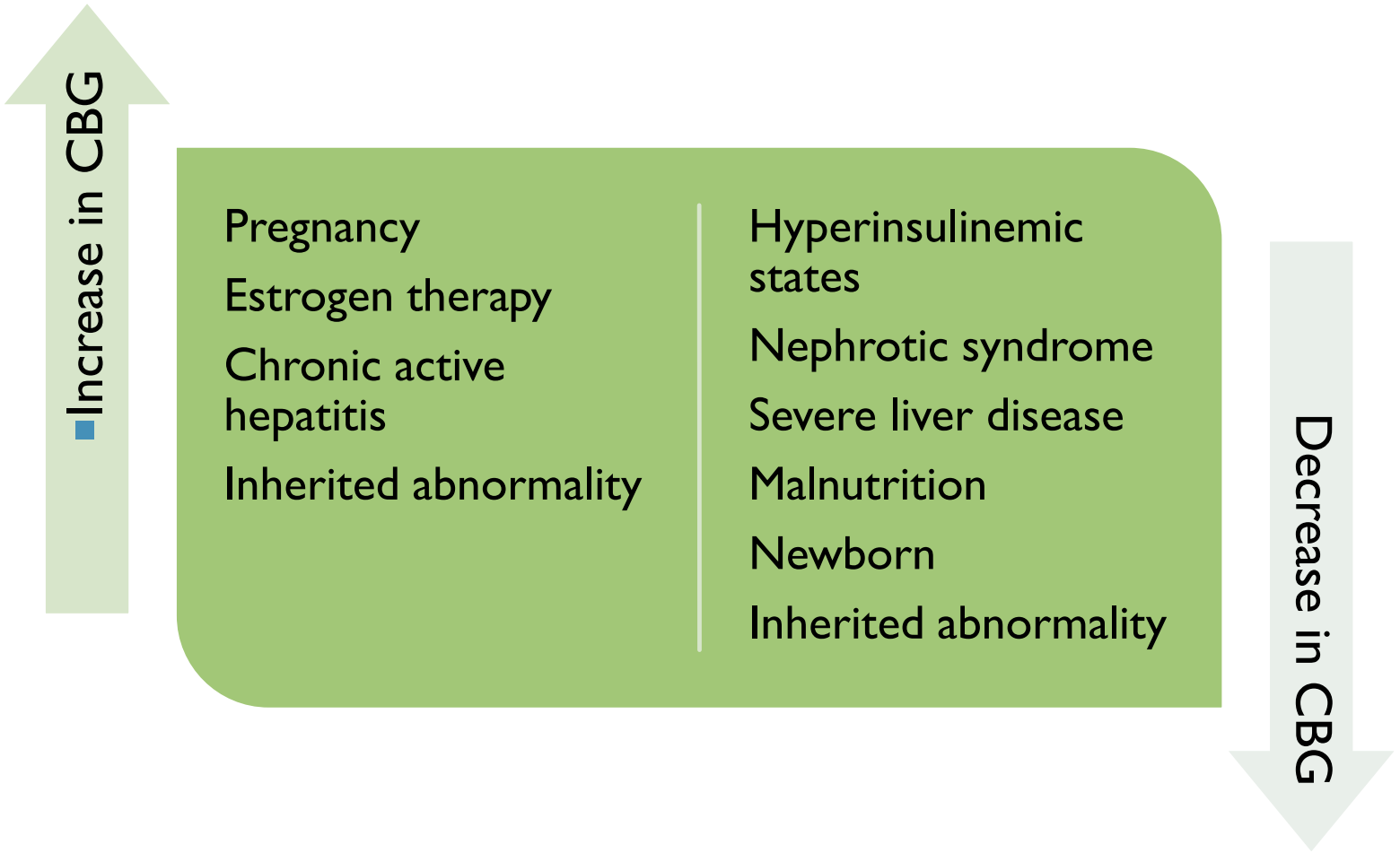
EL-FARHAN N, PICKETT A, DUCROQ D, ET AL. METHOD-SPECIFIC SERUM CORTISOL RESPONSES TO THE ADRENOCORTICOTROPHIN TEST: COMPARISONOF GAS CHROMATOGRAPHY-MASS SPECTROMETRY AND FIVE AUTOMATED IMMUNOASSAYS. CLIN ENDOCRINOL (OXF). 2013;78:673–680.

Assay-Specific Estimated Lower Reference Limits for Post-Adrenocorticotropin Cortisol According to Gender and Oral Contraceptive Pill (OCP)-Status

Assay	Males	Non-OCP females	Combined male and Non-OCP female subjects*	OCP females
GC-MS	418	421	420	643
Centaur	448	446	446	619
Architect	430	416	NA	577
E170	574	524	NA	791
Immulite (2000)	469	478	474	688
Access	459	455	NA	604

EL-FARHAN N, PICKETT A, DUCROQ D, ET AL. METHOD-SPECIFIC SERUM CORTISOL RESPONSES TO THE ADRENOCORTICOTROPHIN TEST: COMPARISON OF GAS CHROMATOGRAPHY-MASS SPECTROMETRY AND FIVE AUTOMATED IMMUNOASSAYS. CLIN ENDOCRINOL (OXF). 2013;78:673–680.

FACTORS THAT INFLUENCE CBG LEVELS



2.0 OPTIMAL DIAGNOSTIC TESTS

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

Stimulated increase of cortisol after 30 or 60 min in healthy individuals is comparable for both 1 mcg and 250 mcg ACTH test.

The low-dose test adds no further sensitivity or specificity over the high-dose test in the diagnosis of PAI.

2.0 OPTIMAL DIAGNOSTIC TESTS- MORNING CORTISOL LEVEL

- 2.3 If a ACTH stimulation test is not feasible, we suggest using a morning cortisol <140 nmol/L (5 mcg/dL) in combination with ACTH as a preliminary test suggestive of adrenal insufficiency (until confirmatory testing with corticotropin stimulation is available)

  - A cut off threshold for basal cortisol concentrations of <140 nmol/L (5 mcg/dL) drawn in the morning (6 to10 AM) is suggestive of adrenal insufficiency.
  - Most reports detailing this cut off value are not based on subjects with PAI.
  - Cortisol level of 5 mcg/dL is at or near the normal limit of the range of normal subjects.

MORNING CORTISOL FOR THE DIAGNOSIS OF AI

Study	Basal cortisol (early morning)			SDCT (30 min/peak)			LDCT (20–30 min)		
	n HPAI/n total	HPAI[a] (μg/dl)	No HPAI[b] (μg/dl)	n HPAI/n total	HPAI[a] (μg/dl)	No HPAI[b] (μg/dl)	n HPAI/n total	HPAI[a] (μg/dl)	No HPAI[b] (μg/dl)
Studies with paired data									
Abdu (22)	13/42	≤3.2	≥12.2	13/42	≤8.6	≥19.1	13/42	≤12.7	≥16.8
Courtney (16)	11/41	≤3.0	≥11.4	11/41	≤17.1	≥22.4	11/41	≤7.1	≥22.1
Gonc (18)	11/29	≤5.7	≥9.0	11/29	≤15.6	≥36.1	11/29	≤15.8	≥18.6
Maghnie (19)	14/24	≤9.1	≥15.0	13/23	≤19.9	≥33.0	14/24	≤19.6	≥22.7
Mayenknecht (11)	NA	NA	NA	23/44	≤16.0	≥32.0	23/44	≤15.8	≥28.0
Talwar (7)[d]	13/24	≤10.0	≥13.5	13/24	≤22.5	≥31.7	13/24	≤17.9	≥21.0
Tordjman (21)	19/62	≤4.8	≥17.9	16/53	≤12.8	≥38.5	19/62	≤13.9	≥17.9
Studies with unpaired data									
Ambrosi (14)	12/57	≤3.6	≥9.3	NA	NA	NA	12/57	≤16.6	≥26.8
Ammari (15)	17/30	≤7.4	≥14.7	17/30	≤17.0	≥33.9	NA	NA	NA
Choi (5)[d]	36/72	≤4.8	≥13.3	NA	NA	NA	36/72	≤15.3	≥18.9
Kane (6)[d]	9/22	≤4.4	≥8.6	9/22	≤12.2	≥15.7	NA	NA	NA
Rose (17)[c]	42/158	≤3.2	≥12.5	14/38	≤16.0	≥39.0	28/120	≤17.5	≥20.5
Soule (20)	13/74	≤3.5	≥18.0	NA	NA	NA	13/74	≤17.0	≥24.5
Mean (95% CI)	33%	≤5	≥13	40%	≤16	≥30	33%	≤16	≥22
	210/635	(4.7–5.3)	(12.9–13.6)	140/346	(15.2–16.4)	(29.9–32.3)	193/586	(15.2–16.0)	(20.9–21.9)

KAZLAUSKAITE R, EVANS AT, VILLABONA CV, ET AL. CORTICOTROPIN TESTS FOR HYPOTHALAMIC-PITUITARY-ADRENAL INSUFFICIENCY: A METAANALYSIS. J CLIN ENDOCRINOL METAB. 2008;93:4245–4253.

2.0 DIAGNOSTIC TESTING- PLASMA ACTH LEVEL

- 2.4 We recommend measurement of plasma ACTH to establish PAI. In patients with confirmed cortisol deficiency, a plasma ACTH >2-fold the upper limit of the reference range is consistent with PAI.
  - A plasma ACTH concentration exceeding 300 ng/L (66 pmol/L) provides maximum stimulation of glucocorticoid synthesis.
  - Difficult to establish a specific cut-point for ACTH levels due to due to analytical bias.
  - Only two studies have reported the ACTH range for PAI at diagnosis with a control reference population, and in these studies the ACTH was typically grossly elevated in PAI.

2.0 DIAGNOSTIC TESTING- PLASMA RENIN AND ALDOSTERONE

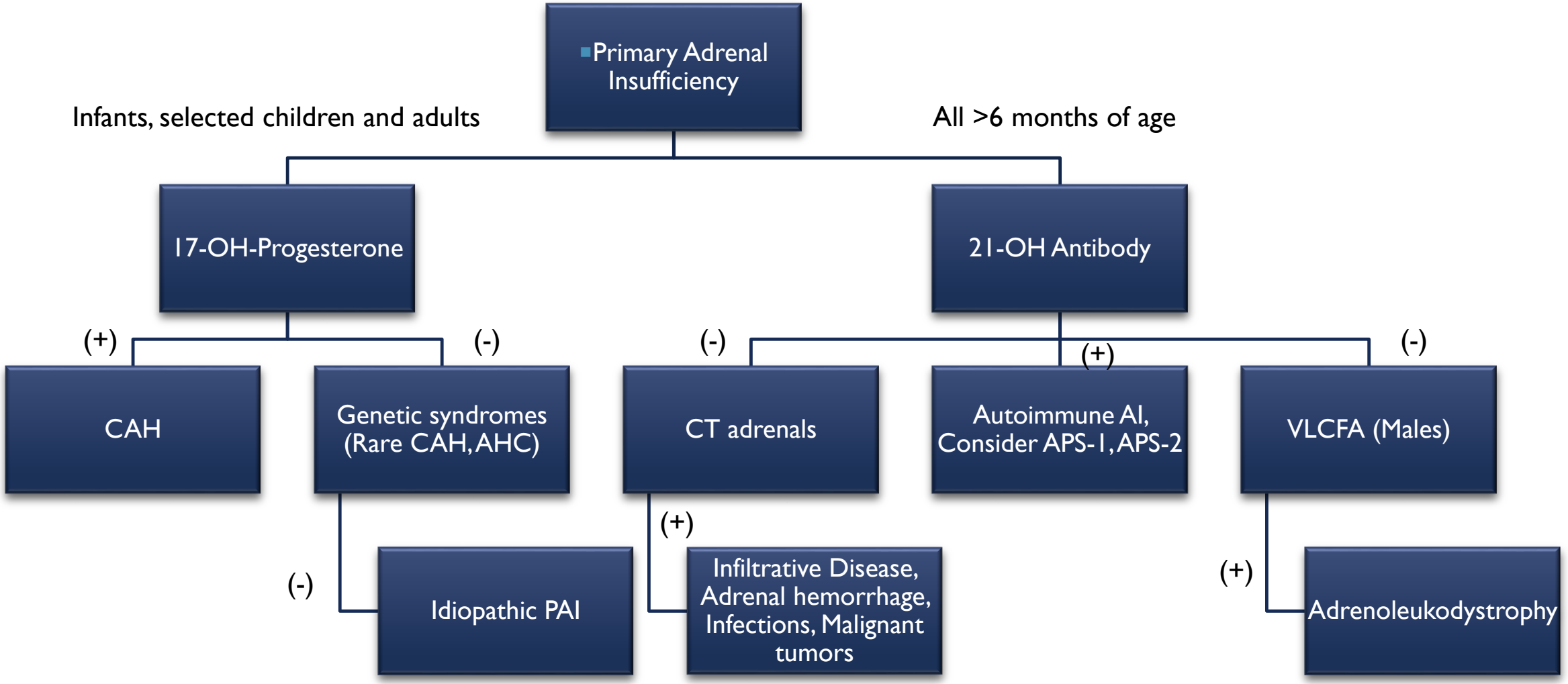
- 2.5 We recommend the simultaneous measurement of plasma renin and aldosterone in PAI to determine the presence of mineralocorticoid deficiency.

- In the early phase of evolving PAI mineralocorticoid deficiency may predominate.
- Some etiologies of PAI does not present mineralocorticoid deficiency.

2.0 DIAGNOSTIC TESTING

- 2.6 We suggest that the etiology of PAI should be determined in all patients with confirmed disease. (Ungraded best practice recommendation)

Algorithm for the diagnostic approach to the patient with PAI



ROLE OF 21-OH ANTIBODIES IN THE DEVELOPMENT OF PAI

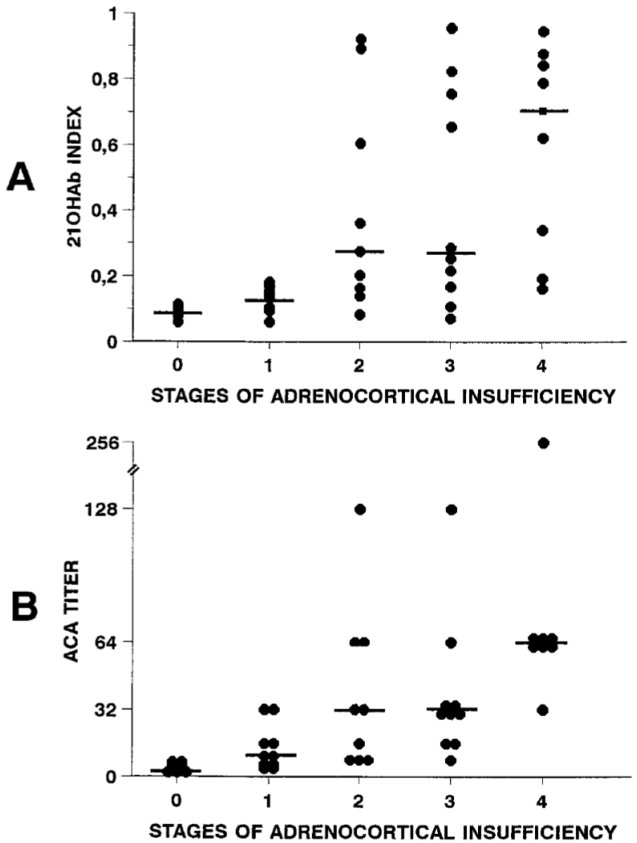
Coco, G., et al. J Clin Endocrinol Metab 91: 1637–1645, 2006

- Assess the contribution of different clinical, immunological, genetic, and functional factors in the progression to AAD.
- 100 ACA-positive and 63 ACA-negative patients without AAD were followed for a maximum of 21 yrs.
- About 30% progressed to overt PAI during a 5-year follow-up.

Laureti S., et al. J Clin Endocrinol Metab 83: 3507–3511, 1998

- Levels of adrenal autoantibodies correlate with the degree of adrenal dysfunction.
- 19 ACA-positive subjects with preclinical Addison's disease.
- The levels of adrenal autoantibodies were positively associated with the severity of adrenal dysfunction (ANOVA, P , 0.0001 for both 21OHAb and ACA).

Levels of Adrenocortical Autoantibodies Correlate with the Degree of Adrenal Dysfunction in Subjects with Preclinical Addison's Disease



- The 21OH index was significantly lower at stage 0 or 1 than at stage 2 + 3 (corrected P, 0.001 and P, 0.05) or stage 4 (corrected P, 0.001 and ,0.01).
- ACA titer at stage 4 was significantly higher than stage 0 (P, 0.001), stage 1 (P, 0.001), and stage 2+3 (P, 0.05); and ACA titer at stage 2+3 was higher than stage 0 (P, 0.001) and stage 1 (P, 0.05).

LAURET IS, DE BELLIS A, MUCCITELLI VI, ET AL. LEVELS OF ADRENOCORTICAL AUTOANTIBODIES CORRELATE WITH THE DEGREE OF ADRENAL DYSFUNCTION IN SUBJECTS WITH PRECLINICAL ADDISON'S DISEASE. J CLIN ENDOCRINOL METAB. 1998;83:3507–3511.

3.0 TREATMENT OF PRIMARY ADRENAL INSUFFICIENCY IN ADULTS GLUCOCORTICOID REPLACEMENT REGIMEN

- 3.1 We recommend glucocorticoid therapy in all patients with confirmed PAI.
- 3.2 We suggest using hydrocortisone (15–25 mg) or cortisone acetate (20–35mg) in two or three divided oral doses per day
- 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.
- 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.

GLUCOCORTICOID REPLACEMENT REGIMENS

Optimal hydrocortisone replacement therapy			
	Twice daily hydrocortisone	Thrice daily hydrocortisone	
Hydrocortisone doses (mg)	20am/10pm	10am/5noon/5pm	10am/10noon/5pm
Optimal replacement (% of pts)	10%	66%	50%
Quality score (1-4)	2.48	3.62	3.32

*'Optimal replacement' was arbitrarily defined as that dose which achieved a UFC and 09:00 h cortisol within the reference range for the normal population (to avoid over-replacement) combined with 1230 h and 1730 h cortisol above 50 nmol/l (1.8 mcg/dl), and ideally above 100 nmol/l (3.6 mcg/dl) (to avoid under-replacement)

HOWLETT TA. AN ASSESSMENT OF OPTIMAL HYDROCORTISONE REPLACEMENT THERAPY. CLIN ENDOCRINOL (OXF). 1997;46:263–268.

GLUCOCORTICOID REPLACEMENT REGIMENS

Mah PM, et al. *Clin Endocrinol* 2004	• Single dose-morning HC adjusted by BSA (5.5 mg/m2) or by weight (0.12 mg/kg) produced integrated cortisol levels over 6 hrs within the healthy control 95% CI.
Laureti, et al 2003 and Barbetta, et al 2005	• Thrice-daily cortisone acetate lowered ACTH levels and gave 24-hour cortisol curves more similar to the endogenous cortisol rhythm compared with a two-dose regimen
Ekman, et al 2012	• Double-blind, randomized, crossover study. Evaluated two-dose vs four-dose regimen with more physiological pharmacokinetics with the four-dose.

3.0 TREATMENT OF PRIMARY ADRENAL INSUFFICIENCY IN ADULTS GLUCOCORTICOID REPLACEMENT REGIMEN

- 3.5 We suggest monitoring glucocorticoid replacement using clinical assessment including body weight, postural blood pressure, energy levels, signs of frank glucocorticoid excess.
- 3.6 We suggest against hormonal monitoring of glucocorticoid replacement and to adjust treatment only based on clinical response.

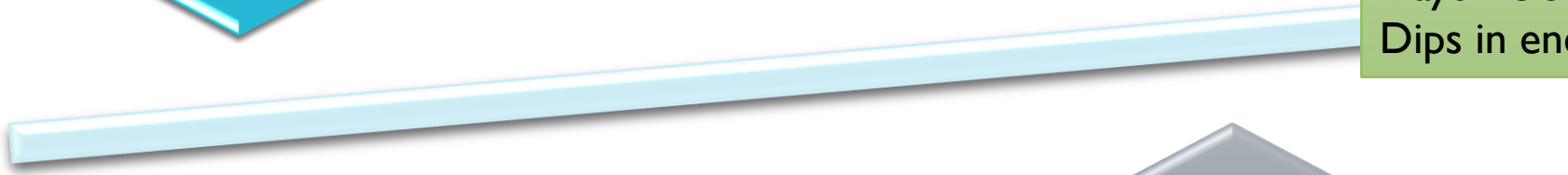
MONITORING GLUCOCORTICOID REPLACEMENT

Over-replacement

- Weight gain
- Insomnia
- Peripheral edema

Detailed questioning…

Daily habits
Working patterns
Energy
Mental concentration
Daytime somnolence
Dips in energy



Under-replacement

- Nausea
- Poor appetite
- Weight loss
- Lethargy
- hyperpigmentation

MINERALOCORTICOID REPLACEMENT IN PAI

- 3.7 We recommend that all patients with confirmed aldosterone deficiency receive mineralocorticoid replacement with fludrocortisone (starting dose, 50–100 mcg in adults) and not restrict their salt intake.
- 3.8 We recommend monitoring mineralocorticoid replacement primarily based on clinical assessment (salt craving, postural hypotension, or edema), and blood electrolyte measurements.
- 3.9 In patients who develop hypertension while receiving fludrocortisone, we suggest reducing the dose of fludrocortisone.
- 3.10 If blood pressure remains uncontrolled, we suggest initiating antihypertensive treatment and continuing fludrocortisone.

MINERALOCORTICOID REPLACEMENT

Assessed clinically

- Salt craving
- Light-headedness
- Blood pressure (sitting and standing)
- Peripheral edema (low sensitivity)

Agents affecting fludrocortisone metabolism

- Licorice
- Grapefruit juice
- Phenytoin

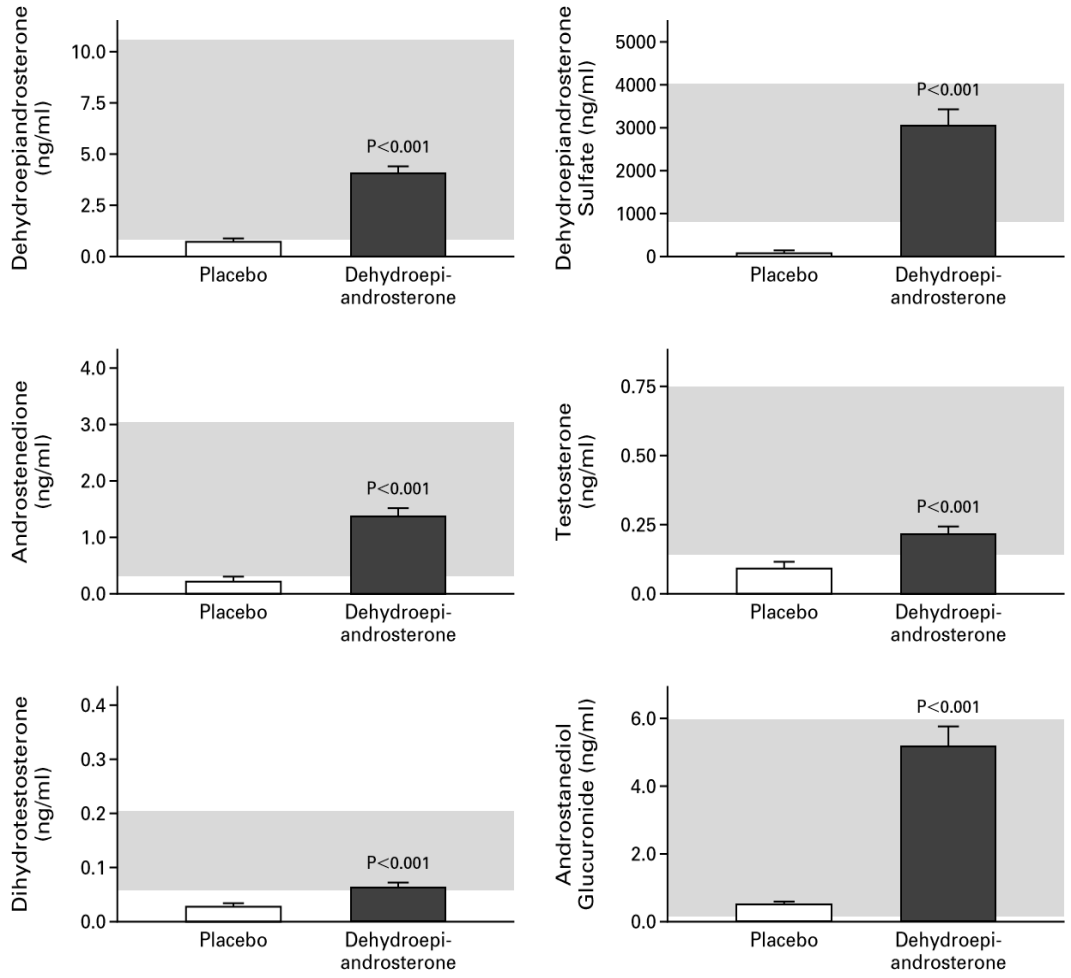
Hypertension

- Evaluate fludrocortisone and glucocorticoid dose
- ACE-I or ARBs preferred
- Avoid diuretics
- Spirinolactone and eplerenone contraindicated

DEHYDROEPIANDROSTERONE REPLACEMENT

- 3.11 We suggest a trial of DHEA replacement in women with PAI and low libido, depressive symptoms, and/or low energy levels despite otherwise optimized glucocorticoid and mineralocorticoid replacement.
- 3.12 We suggest an initial period of 6 months of DHEA replacement. If the patient does not report a sustained, beneficial effect of replacement after 6 months, the DHEA should be discontinued.
- 3.13 We suggest monitoring DHEA replacement by measuring morning serum DHEAS levels (aiming at the mid normal range) before the intake of the daily DHEA replacement dose.

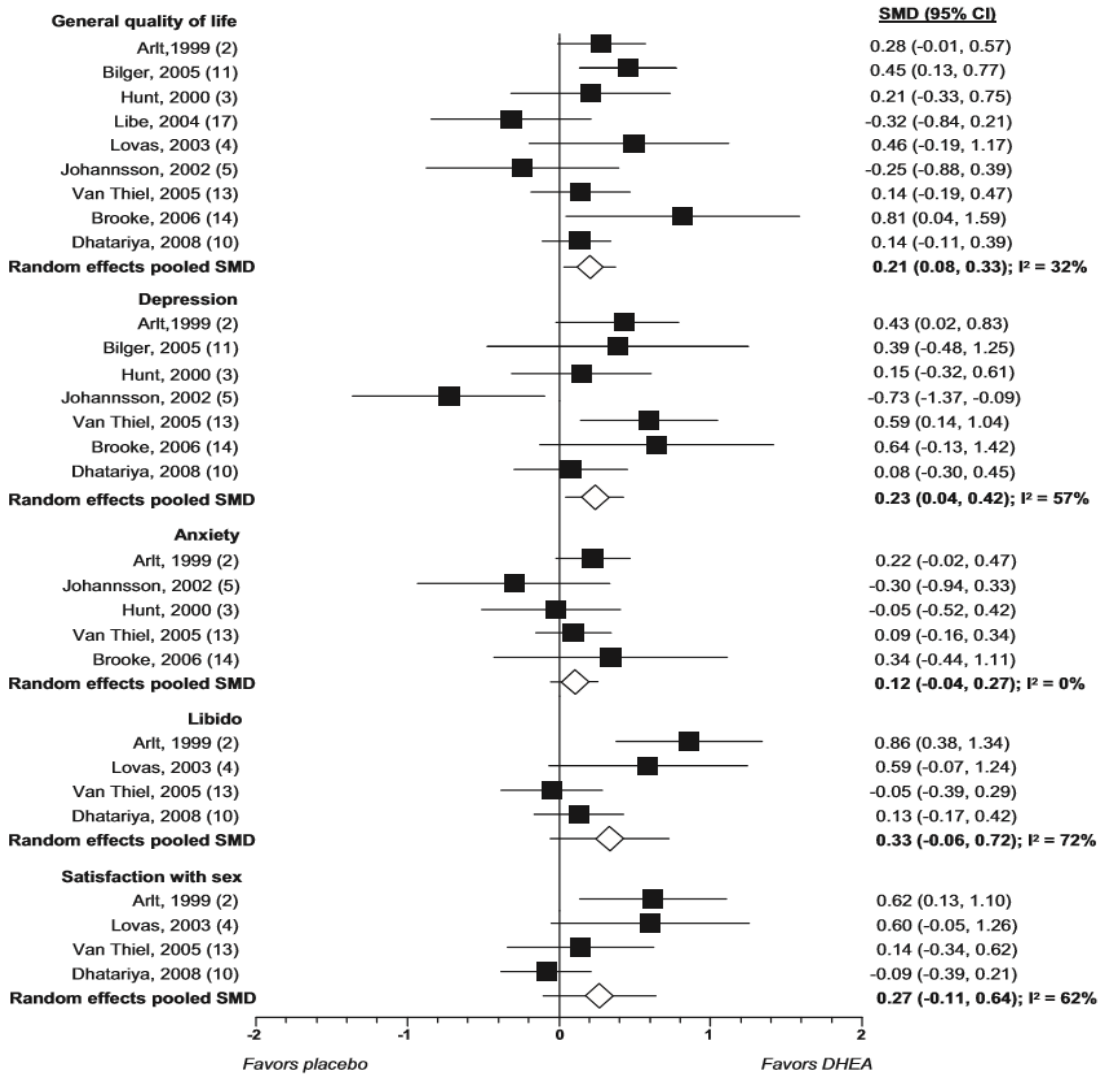
DEHYDROEPIANDROSTERONE REPLACEMENT



- Double-blind study
- 24 women with adrenal insufficiency
- 50 mg of DHEA orally each morning for four months and placebo daily for four months, with a one-month washout period.
- DHEA significantly improved overall well-being as well as scores for depression and anxiety. Also improved sexuality.

ARLT W, CALLIES F, VAN VLIJMEN JC, ET AL. DEHYDROEPIANDROSTERONE REPLACEMENT IN WOMEN WITH ADRENAL INSUFFICIENCY. N ENGL J MED. 1999;341:1013–1020.

Random-effects meta-analysis of DHEA on HRQoL, depression, anxiety, and sexual function



ALKATIB AA, COSMA M, ELAMIN MB, ETAL.. J CLIN ENDOCRINOL METAB. 2009;94:3676–3681.

TREATMENT DURING PREGNANCY

- 3.14 Monitor clinical symptoms in pregnant patients with PAI for over- and under-replacement with at least one review per trimester.
- 3.15 Increase dose of hydrocortisone in particular during the 3rd trimester based on clinical course.
- 3.16 Use hydrocortisone over cortisone acetate, prednisolone, or prednisone. Do not use dexamethasone.
- 3.17 Hydrocortisone stress dosing during the active phase of labor.

NORMAL CORTISOL VARIATION DURING PREGNANCY

- 1st to 2nd trimester
  - Increase in CBG
  - Increase in cortisol

- 2nd Trimester
  Week 22
  - Increase in free cortisol

- 3rd Trimester
  Preterm
  - Further rise in free cortisol
  - Fall in CBG

CORTISOL RESPONSE TO ACTH DURING PREGNANCY

Diagnostic cortisol cutoffs after ACTH stimulation test	
First trimester	25 mcg/dL
Second trimester	29 mcg/dL
Third trimester	32 mcg/dL

LEBBE M, ARLT W. WHAT IS THE BEST DIAGNOSTIC AND THERAPEUTIC MANAGEMENT STRATEGY FOR AN ADDISON PATIENT DURING PREGNANCY? CLIN ENDOCRINOL (OXF). 2013;78:497–502.

TREATMENT AND MONITORING DURING CHILDHOOD

- 3.18 Hydrocortisone in 3 to 4 divided doses (total starting daily dose of 8 mg/m2 BSA)
  - No published RCT of various treatment regimens for PAI in children.
  - No data are available to compare the long-term effects of various formulations of glucocorticoid.
- 3.19 Avoid synthetic, long acting glucocorticoids (prednisolone, dexamethasone)
  - Hydrocortisone has a short half-life and is easier to titrate.
  - Cortisone may be used but understand that activity of 11ß-hydroxysteroid dehydrogenase type 1 activity is variable
  - Most data available are in children with CAH

MONITORING GLUCOCORTICOID REPLACEMENT IN CHILDREN

Overtreatment

- Excessive weight gain
- Decreased height velocity
- Signs or symptoms of Cushing's

Underreplacement

- Inadequate weight gain
- Fatigue
- Anorexia
- Hyperpigmentation

- In patients with CAH, GC doses >20mg/m2/d in infants and >15-17mg/m2/d in adolescents result in loss of height and shorter adult stature

BONFIG W, ET AL. J CLIN ENDOCRINOL METAB. 2009;94:3882–3888.
GRIGORESCU-SIDO A, ET AL. HORMONES.2003; 60:84–90.

MINERALOCORTICOID REPLACEMENT IN CHILDREN

- 3.21 In children with PAI and confirmed aldosterone deficiency, we recommend treatment with fludrocortisone (starting dosage, 100 mcg/d). For infants, we recommend sodium chloride supplements in the newborn period and up to the age of 12 months.

MINERALOCORTICOID REPLACEMENT IN CHILDREN

- Mineralocorticoid dose does not require adjustment by BSA.

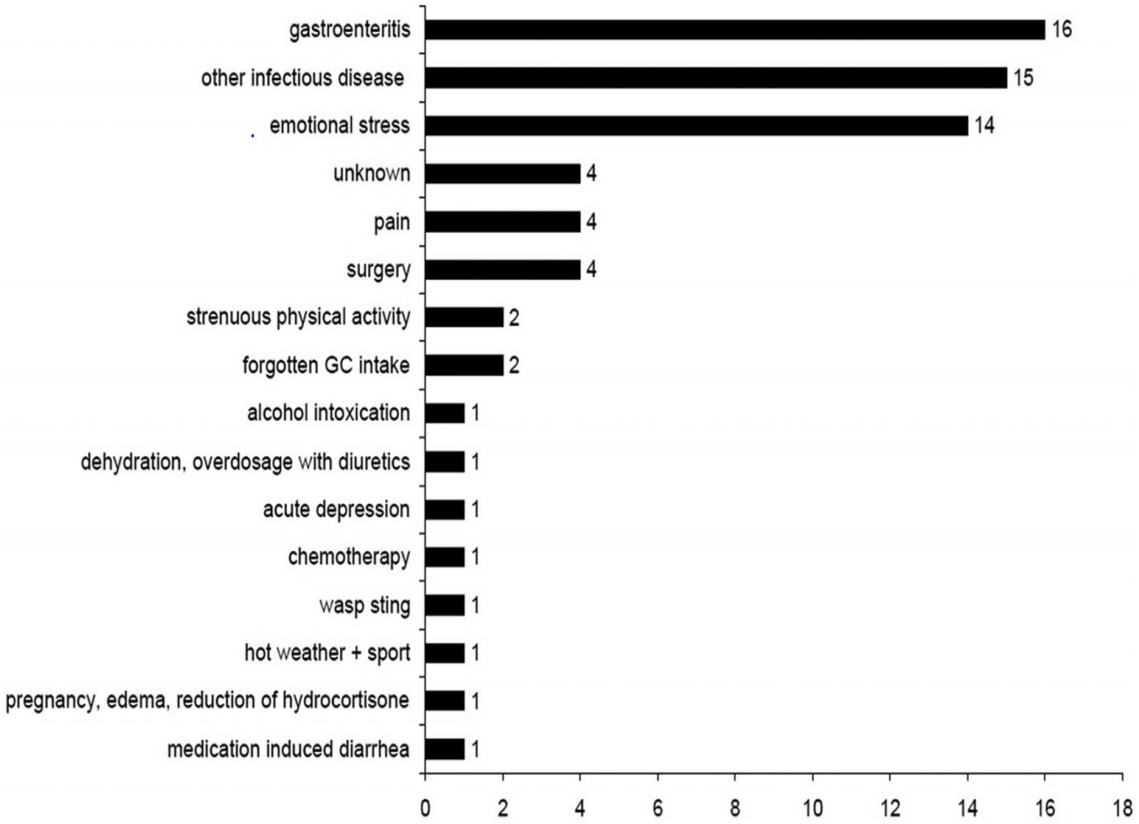
For infants, sodium chloride 1-2 g/d due to mineralocorticoid resistance of the immature kidney.

Dose adjusted based on signs and symptoms of inadequate replacement and renin levels.

Infants require evaluation every 3 to 4 months to assess growth, blood pressure, and general well being.

4.0 MANAGEMENT AND PREVENTION OF ADRENAL CRISIS

Precipitating factors for adrenal crisis



- 423 patients were followed up for 2 years (221 pts had PAI)
- Precipitating factors of adrenal crisis in 46 patients during a prospective follow-up analysis. Multiple answers were possible.
- 8.3 crises per 100 patient-years
- Ten patients died during follow-up; in four cases death was associated with AC (0.5 AC related deaths per 100 patient-years).

HAHNER S, ETAL. HIGH INCIDENCE OF ADRENAL CRISIS IN EDUCATED PATIENTS WITH CHRONIC ADRENAL INSUFFICIENCY: A PROSPECTIVE STUDY. J CLIN ENDOCRINOL METAB. 2015;100:407–416.

Management of PAI in Specific Situations (Adults)	
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	IM or SC hydrocortisone 100 mg
Minor to moderate surgical stress	Hydrocortisone, 25–75 mg/24 h (usually 1 to 2 d)
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). 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

ALLOLIO B. EXTENSIVE EXPERTISE IN ENDOCRINOLOGY: ADRENAL CRISIS. EUR J ENDOCRINOL. 2015;172:R115–R124.

Management of PAI in Specific Situations (Children)	
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	IM hydrocortisone 50 mg/m2 or estimate; infants, 25 mg; school-age children, 50 mg; adolescents, 100 mg
Minor to moderate surgical stress	IM hydrocortisone 50 mg/m2 or hydrocortisone replacement doses doubled or tripled
Major surgery with general anesthesia, trauma, or disease that requires intensive care	Hydrocortisone 50 mg/m2 iv followed by hydrocortisone 50–100 mg/m2/d divided q 6h. 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 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/m2 bolus followed by hydrocortisone 50–100 mg/m2/d dividedq6h

ALLOLIO B. EXTENSIVE EXPERTISE IN ENDOCRINOLOGY: ADRENAL CRISIS. EUR J ENDOCRINOL. 2015;172:R115–R124.

Measures for Prevention of Adrenal Crisis

- Identify and define the problem

Steroid emergency card (check that card is available and up to date)

Medical alert bracelet or necklace: "Adrenal insufficiency – needs steroids!"

Educate patient (and partner/parents)

Sick day rule 1: need to double the routine oral glucocorticoid.

Sick day rule 2: need to inject a glucocorticoid preparation IM or IV

Give special attention to:

Explaining the rationale for dose adjustment in stress/sickness.

Discussing the situations requiring dose adjustment.

Discussing symptoms and signs of emergent adrenal crisis.

Teaching parenteral self-administration of glucocorticoid preparation.

Enforcing the need to go to hospital after emergency injection.

BANCOS, ET AL: DIAGNOSIS AND MANAGEMENT OF ADRENAL INSUFFICIENCY. LANCET DIABETES ENDOCRINOL. 2015;3:216–226

Measures for Prevention of Adrenal Crisis

Provide patient with:

- Sufficient supply of hydrocortisone and fludrocortisone (accounting for possible sick days)
- Hydrocortisone emergency injection kit prescription (vials of 100 mg hydrocortisone sodium, syringes, needles)
- Leaflet with information on adrenal crisis and hospitalization to be shown to health care staff

Follow up:

- Reinforce education and confirm understanding during each follow-up visit

BANCOS, ET AL: DIAGNOSIS AND MANAGEMENT OF ADRENAL INSUFFICIENCY. LANCET DIABETES ENDOCRINOL. 2015;3:216–226

IMPORTANT

MEDICAL INFO

THIS PATIENT NEEDS DAILY REPLACEMENT THERAPY WITH CORTISONE

In case of serious illness, trauma, vomiting or diarrhea, hydrocortisone 100 mg iv/im and iv saline infusion should be administered **WITHOUT DELAY**.

Name

Personnumber/Date of birth

European Society of Endocrinology

Existing cards

MEDICAL ALERT BRACELET

Pre-engraved "Adrenal Insufficiency" Medical Alert Identification Star of Life Marsala Designer bracelet.

2

$21.95

Add to Cart

Black Silicone Sport Medical Alert ID Bracelet. Incl. 6 lines of personalized engraving.

215

$24.95

Add to Cart

Pre-engraved "Adrenal Insufficiency" Medical Alert Identification Star of Life Black Designer bracelet.

4

$21.95

Add to Cart

Medical I.D Bracelet

179

$9.99 - $13.95

See all buying options

Waterproof ELITE USB black silicone medical alert ID bracelet with 2 GB USB (Black)

55

$36.95 Prime

Add to Cart

Pre-engraved "Adrenal Insufficiency" Medical Alert Identification Black Advisor/Slim bracelet.

4

$21.95

Add to Cart

Pre-engraved Acrylic Plate "Adrenal Insufficiency" Elite Medical Alert Identification Bracelet - PINK. Choose from Diabetes, Blood

$27.95

Add to Cart

Suggested Follow-up Routines For Patients With AI

History

- [ ] History focused on well-being, capacities in work and social life; sexuality, fertility, adrenal crises
- [ ] How much and when medication is taken
- [ ] Symptoms and signs of over and under replacement

Physical examination

- [ ] Weight
- [ ] Blood pressure sitting/supine and standing
- [ ] Look for pigmentation changes, alopecia, vitiligo, goiter, and Cushingoid side effects

HUSEBYE AE., ADRENAL INSUFFICIENCY: INDIVIDUALIZED MANAGEMENT. 2016 MEET THE PROFESSOR: ENDOCRINE CASE MANAGEMENT. P24

Suggested Follow-up Routines For Patients With AI

Recommended annual tests

- [ ] CBC, Na, K, creatinine, ferritin and cobalamin
- [ ] TSH, free T4, anti-TPO,
- [ ] HbA1c
- [ ] Renin/renin activity

Other tests

- [ ] Serum or salivary cortisol day curve to check bioavailability
- [ ] Vitamin B12 def? methylmalonic acid, parietal cell and intrinsic factor abs
- [ ] Celiac disease? Transglutaminase abs and total IgA (once)
- [ ] Osteoporosis: DXA scan at start of follow up, around menopause depending on clinical situation

HUSEBYE AE., ADRENAL INSUFFICIENCY: INDIVIDUALIZED MANAGEMENT. 2016 MEET THE PROFESSOR: ENDOCRINE CASE MANAGEMENT. P24

PERSPECTIVES AND DEMAND FOR FUTURE RESEARCH

Diagnostic procedures

*Dx procedures and tx strategies are still far from being optimal

Salivary cortisol

- Potential biomarker
- Limitation- collection and analysis perspectives

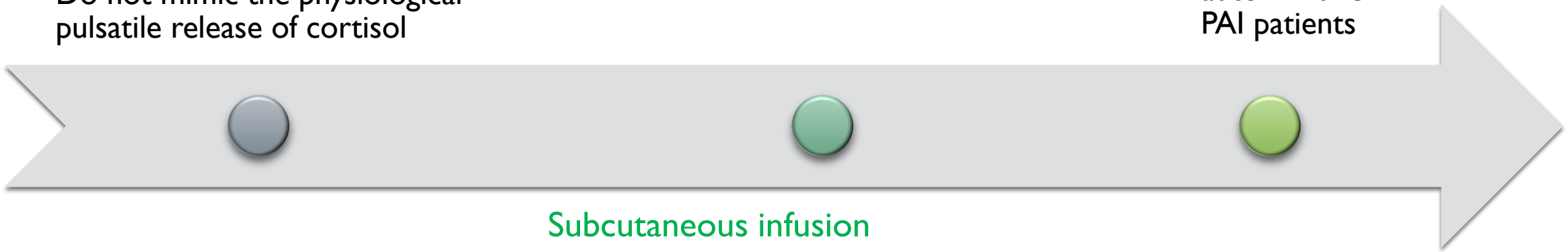
Cortisol by LC-MS/MS

- Better standardization
- Free from analytical interference
- No cross-reactivity issues seen with IMA
- Ability to quantify multiple steroids

PERSPECTIVES AND DEMAND FOR FUTURE RESEARCH

Dual and slow-release formulations of hydrocortisone

- Aimed to mimic the cortisol circadian rhythm
- Do not mimic the physiological pulsatile release of cortisol



Subcutaneous infusion

- Circadian rhythm
- Mimic early morning increase in cortisol
- Improvement in HRQoL?
- ACTH could be used as a biomarker

Rituximab

- Newly diagnosed autoimmune PAI patients