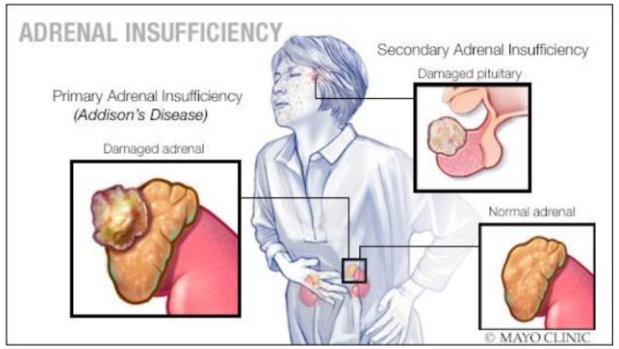

Adrenal Insufficiency

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Disclosures

- No conflict of Interest to Report

Objectives

- Review pathogenesis and clinical presentation
  - Cortisol deficiency
- Review principles of diagnosis and therapy for each conditions

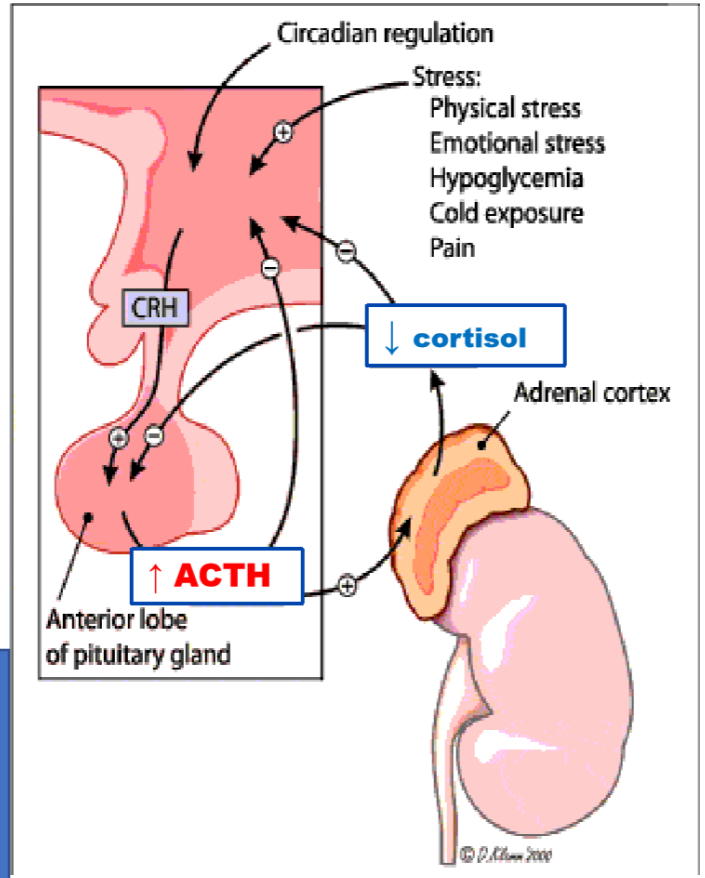
A 64-year-old has been taking steroids for asthma for 5 years. She undergoes urgent surgery for a perforated ulcer. Two days later, she becomes hypotensive, febrile, and hypoglycemic. What is the most likely diagnosis?

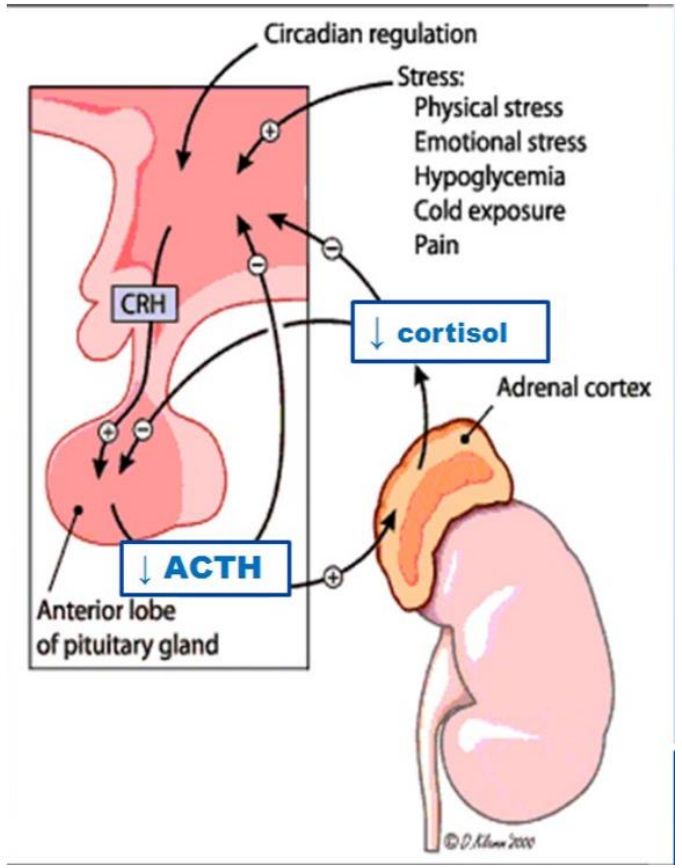
A. Adrenal insufficiency
B. Sepsis
C. Hypovolemia
D.Steroid induced diabetes

Hypothalamic- pituitary axis

Primary adrenal insufficiency

Adrenal gland Disease → low glucocorticoid level -> feed back High ACTH level





Tertiary adrenal insufficiency

Inadequate CRH production by the hypothalamus (rare)

Secondary adrenal insufficiency

Pituitary gland Disease →decrease production of ACTH level

Causes of Cortisol Deficiency

Most common is iatrogenic

- All exogenously administered glucocorticoids regardless of dose or route of administration may suppress the HPA axis
- Endogenous cortisol will suppress in 50% of patients who receive intra-articular or oral GC and 5-10% of patient who received inhaled or topical GC

A 27-year-old female patient is 1-month postpartum. She has symptoms of anorexia, weight loss, hyperpigmentation, bowel changes, and lightheadedness on standing. The cosyntropin stimulation test shows random serum cortisol is 11 micrograms/dL. Serum cortisol 1 hour after 0.25 mg cosyntropin is 14 micrograms/dL.

What is the most likely etiology of this patient's illness?

A. Pituitary tumor
B. Autoimmune disease
C. Cushing syndrome
D. Tuberculosis

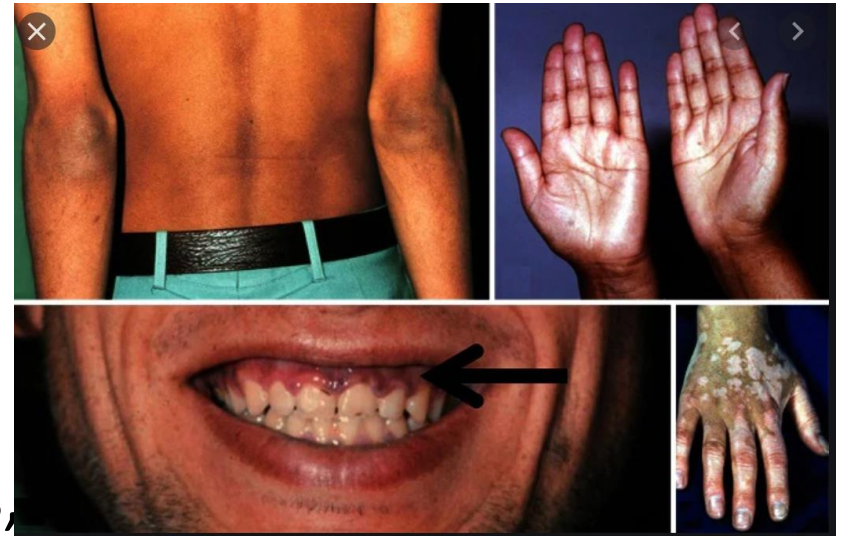
Causes Of Primary Adrenal Insufficiency

Cause	
Autoimmune (80-90% of cases in western countries)- Addison disease	Isolated (30-40%) APS type 1 (5-10%) –AIRE mutations (transcription factor preventing autoimmunity) APS type 2 (60%)
Compression/replacement of normal adrenal tissue	Bilateral adrenal metastasis (lung, breast, colon)
Infection	Tuberculosis, HIV, cytomegalovirus, fungal
Hemorrhage / necrosis / thrombosis	Thrombocytopenia, trauma, lupus, antiphospholipid syndrome, panarteritis nodosa, anticoagulant treatment, tyrosine kinase inhibitors
Infiltration	Sarcoidosis, amyloidosis, hemochromatosis, histiocytosis, lymphoma
Surgery/Trauma	Bilateral Adrenalectomy
Monogenic	congenital adrenal hyperplasia (21OH, 3betahydroxysteroid dehydrogenase, 17alphaOH, X-linked adrenoleukodystrophy or adrenomyeloneuropathy

Primary Autoimmune Adrenal Insufficiency

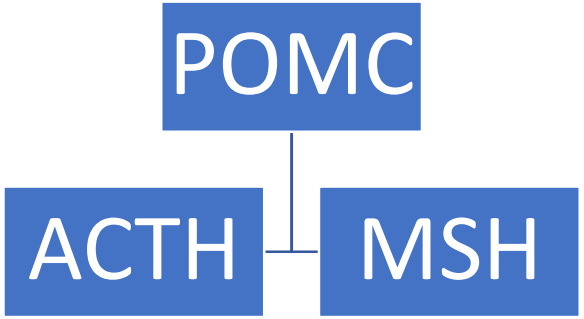
- Prevalence of 100-140 cases per million
- Incidence of around 5-10 cases/ year/million
- Autoimmune destruction of adrenal tissue is the most common cause of primary AI accounting for 68-94% cases (other causes include infection, genetic, bilateral adrenalectomy etc). Can Develop slowly over many years
- Onset: usually between 30 and 50 years
- Female predominance
- Concomitant autoimmune disease occurs in 2/3 of patients
- Family history of Addison's disease can be seen in up to 10% of patients
- Screening of patients with immune mediated diabetes and autoimmune thyroid disorder for anti-adrenal antibodies
- Antibody to Order:
  - 21-OH antibodies are present in more than 90% of autoimmune AI and their detection almost always precedes the onset of disease

Symptoms of Primary ai



- Weight loss is a common presenting sign
- Hyperpigmentation of the buccal mucosa, gums, beds, with primary AI
- Non-specific symptoms such as weakness, fatigue and anorexia.
- GI symptoms such as nausea, vomiting, abdominal pain , or constipation
- Psychiatric symptoms and orthostatic symptoms
- Arthralgia, myalgia and salt craving

Hyperpigmentation due to Increase proopiomelanocortin (POMC)→ this is a prohormone cleaved to ACTH and melanocyte stimulation hormone MSH→increase melanin production

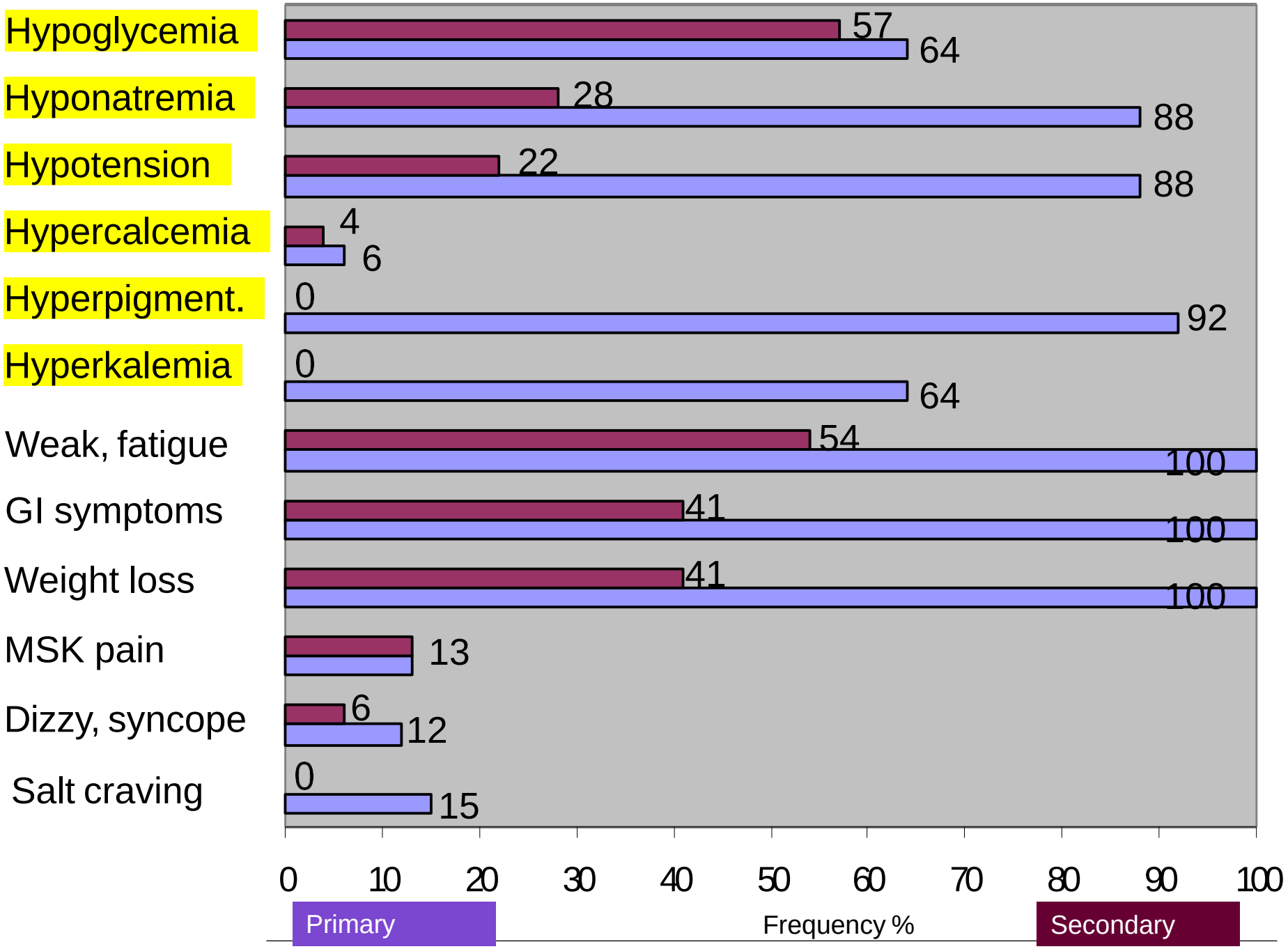


Concomitant Diseases Associated with AI (APS)

Associated condition	APS type 2	APS type 1 (AIRE)
Autoimmune thyroid disease	**25-68%**	2-11%
Premature ovarian failure	**7-21%** in women	17-50%
Type 1 diabetes mellitus	1-15%	2-12%
Atrophic gastritis	8-29%	13-15%
Pernicious anaemia/Vit. B 12 deficiency	5-12%	13-15%
Celiac disease / malabsorption	1-4%	15-22%
Vitiligo	6-14%	8-15%
Alopecia	2-6%	29-37%
Sjögren Syndrome	1-2%	12%
Chronic autoimmune hepatitis	0.5-1%	12-20%
Chronic mucocutaneous candidiasis	NR	73-100%
Primary hypoparathyroidism	1-2 %	76-93%
Dental enamel hypoplasia	NR	77-82%
Keratoconjuctivitis	**NR**	8-41%

Adrenal insufficiency

Metabolic effects of adrenal disorders		
	Cushing syndrome (hypercortisolism)	Addison disease (hypoadrenalism)
Potassium	Low	High
Blood pressure	High	Low
Glucose	High	Low
Leukocytosis	Neutrophilia	Eosinophilia
Imbalance	Metabolic alkalosis	Metabolic acidosis


Hypoglycemia
57
64
Hyponatremia
28
88
Hypotension
22
88
Hypercalcemia
4
6
Hyperpigment.
0
92
Hyperkalemia
0
64
Weak, fatigue
54
100
GI symptoms
41
100
Weight loss
41
100
MSK pain
13
Dizzy, syncope
6
12
Salt craving
0
15
0
10
20
30
40
50
60
70
80
90
100
Primary
Frequency %
Secondary

Imaging abnormalities

- Primary: bilateral adrenal enlargement or masses particular when enlargement is with the normal contour of the adrenal glands
- Atrophic adrenals
  - Secondary: pituitary or sellar mass
- Calcifications – tuberculosis
- Bleeding- hx of anticoagulation use, malignancy, coagulation disorders
- Tumors
- Most times images **cannot rule in or out** the diagnosis and cannot tell if primary or secondary AI.

Causes Of Secondary Adrenal Insufficiency

Cause	
Autoimmune	Lymphocytic hypophysitis (rare), may occur in relation to pregnancy
Compression/replacement of normal adrenal tissue	Pituitary adenoma, craniopharyngioma, meningioma,
Infection	
Hemorrhage / necro	setting of pituitary
Infiltration	dosis, amyloidosis,
Surgery/Trauma	land, traumatic
Genetic	Combined pituitary hormone deficiency variants, isolated ACTH deficiency
Medications	Steroids, **immunotherapy (ICI)**, opioids

Most common cause of Secondary is withdrawal of glucocorticoid after long term use

-Oral

Hydrocortisone, prednisone, dexamethasone, Megestrol acetate

-Inhaled – oral or nasal

-**Joint Injections**

-Topical

A 40-year-old female with a history of HIV and hypertension was brought to the emergency department by her son as she was confused for the past 2 days. She also has been complaining of severe diffuse abdominal pain with nausea and vomiting. Her home medication included megestrol acetate and triumeq (each tablet contains 50 mg dolutegravir, 600 mg abacavir, and 300 mg lamivudine). As per her son, the patient ran out of medication around 2 weeks ago. On physical exam, she was confused. The abdominal exam revealed diffuse tenderness, without rebound tenderness. She had normal deep tendon reflexes. The patient was hypotensive, tachycardiac with hyponatremia, hyperkalemia, and anemia in her laboratory testing. Intravenous fluids were started along with broad-spectrum antibiotics however the patient remained hypotensive requiring vasopressors.

Which of the following is true regarding the patient 's medical condition?

A. The use of triumeq precipitated this medical condition

B. HIV is not considered a risk factor for this condition

C. The use of megestrol acetate precipitate this medical condition

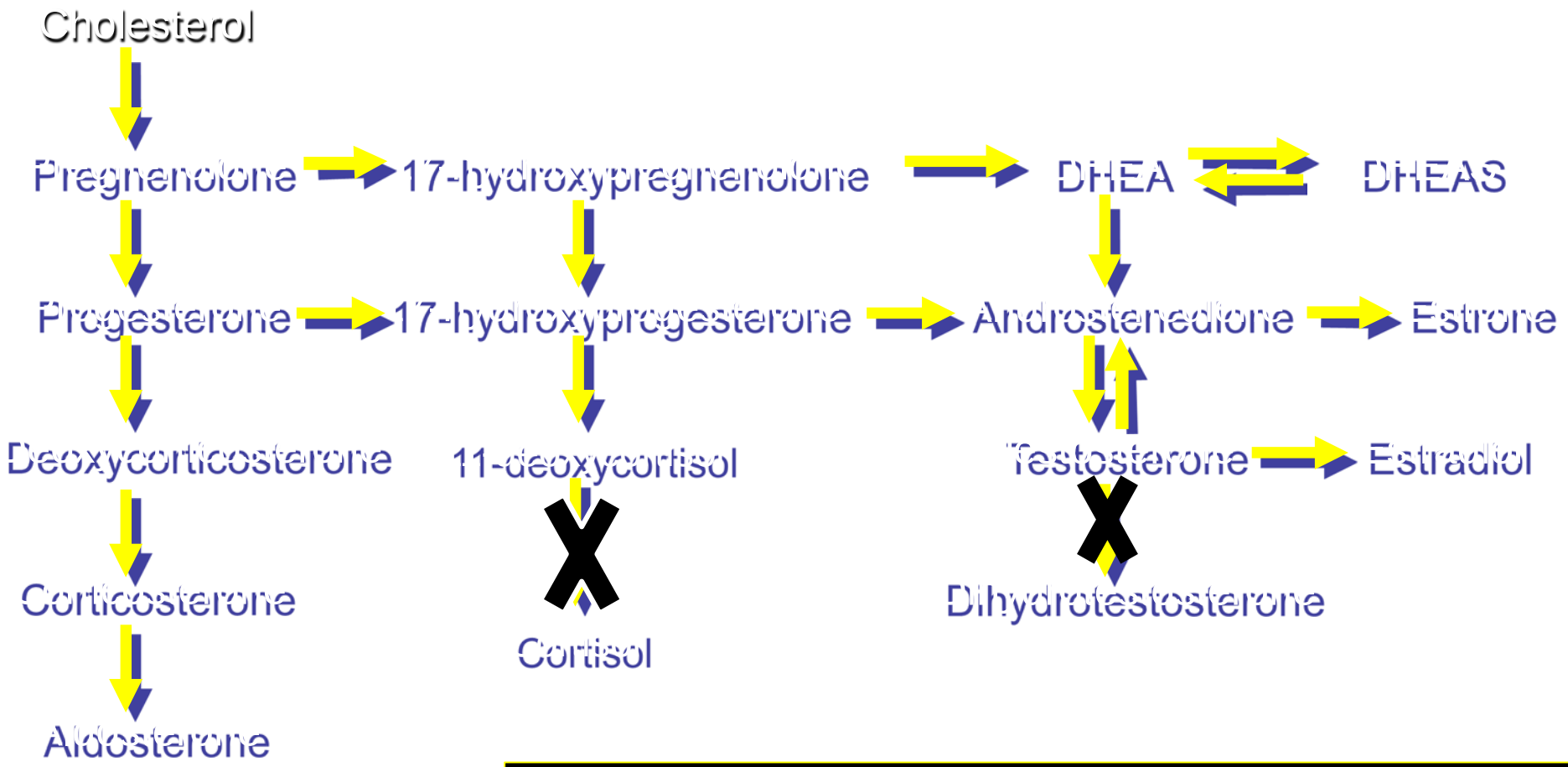
D. There is a decrease in interleukin 1 and 6

What Drugs Cause AI ?

- Glucocorticoids (injection, inhaled, topical, oral)
  - Such as : 20 mg prednisone x 5 days or physiological dose x 1 month
  - Protease inhibitors and other drugs that slow the metabolism of glucocorticoid via interaction with CYP3A4 enzyme (HAART plus inhale steroids)
- High dose progestins such as megestrol acetate/Megace (Appetite stimulant), medroxyprogesterone acetate (MPA)→ both have enough glucocorticoid activity to suppress HPA axis
- Opiates
- Azoles (antifungals)
- Anesthetic etomidate
- Antiparasitic suramin
- Steroids synthesis inhibitors such as aminoglutethimide, metyrapone, mitotane
- **Immune check point inhibitor (Primary or Secondary)**

Mifeprostone (progesterone antagonist and glucocorticoid receptor antagonist) can cause symptoms of AI without concomitant low serum cortisol level

Azole drugs and Primary Adrenal Insufficiency



At high doses, azole drugs can inhibit cortisol synthesis
Keto > Flu > Itraconazole

36-year-old Latino male diagnosed with AIDS after presenting with disseminated histoplasmosis at local hospital (CD4 27, viral load 780K).

Started on Kaletra (lopinavir/ritonavir) and tenofovir/emtricitabine for HIV.

Started on itraconazole therapy for histoplasmosis.

PMH: asthma

Meds: azithromycin q week, dapsone, itraconazole (200 mg bid), Kaletra, tenofovir/emtricitabine

Social History: social alcohol, distant use of marijuana and cocaine, works in McDonald's

Family History: non-contributory

Follow-up: discovered patient using fluticasone inhaler

Patient complains of afternoon fatigue

Further Evaluation:

Denies: nausea, poor appetite, weight loss or gain, orthostatic symptoms, stretch marks, hypertension, acne

PE unremarkable

AM serum cortisol drawn →undetectable

250 mcg ACTH stimulation:

- Baseline cortisol<1
- 30 min cortisol <1
- 60 min cortisol →1.2 mcg/dL

ACTH level 5.4 pg/ml

TSH 1.38 mcIU/mL

Synthetic glucocorticoid screen negative

What are the possible causes of AI on this patient

Differential Diagnosis

Adrenal Insufficiency:

- Disseminated histoplasmosis
  - primary or central adrenal insufficiency
- Itraconazole therapy
  - primary adrenal insufficiency
- Fluticasone/itraconazole interaction
  - central adrenal insufficiency
- Fluticasone/ritonavir interaction
  - central adrenal insufficiency
- HIV
  - primary adrenal insufficiency

Inhaled Glucocorticoid Potency

- Fluticasone = mometasone
- Budesonide = beclomethasone
- Triamcinolone = flunisolide

Healthy volunteers: ritonavir 200 mg/d and fluticasone nasal spray 200ug/d

-Significant increase in area under the curve for fluticasone and a significant decrease (86%) in plasma cortisol AUC within 7 days

Gulliver and Eid, Immunol Allergy Clin North Am, 2005 Glaxo Smith Kline 2003

Case 1 – course of treatment

- Fluticasone discontinued; beclomethasone started
- Hydrocortisone replacement therapy started

Evaluation 1 month later

- AM serum cortisol – 8.5 ug/dl
- 250 mcg ACTH stimulation test – Baseline cortisol -- 5.3 ug/dl

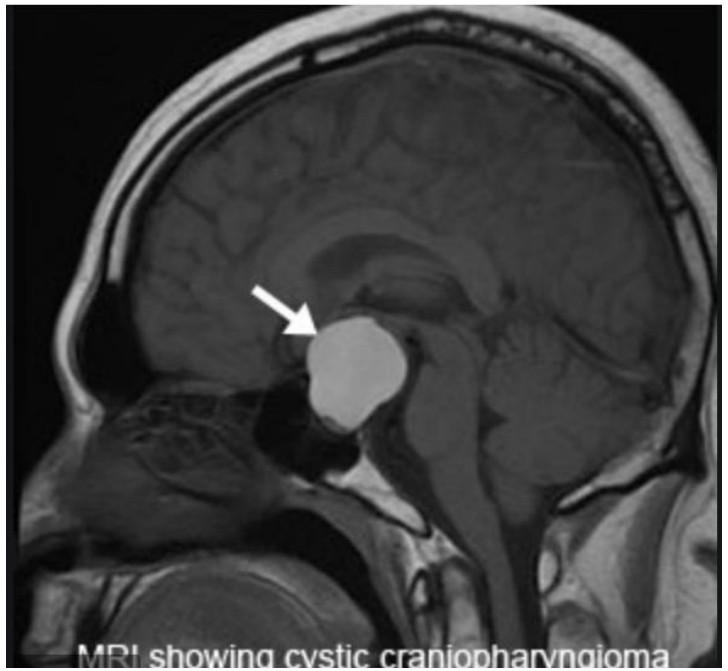
  30 min cortisol – 14.2 ug/dl

  60 min cortisol – 18.0 ug/dl

RECOVERY TIMES ARE VARIABLE

Causes of 2˚ Adrenal Insufficiency

1. Exogenous glucocorticoids
2. Exogenous glucocorticoids
3. Exogenous glucocorticoids
4. Hypothalamic/pituitary disease



Secondary adrenal insufficiency
(low–normal ACTH, low cortisol, normal renin and aldosterone, low DHEAS, low sodium)

↓

MRI pituitary gland

↓

Positive → Hypothalamic-pituitary lesions: pituitary macroadenoma, craniopharyngioma, metastasis

Negative →

- Review drugs (current or recent steroid use, including inhaled, topical, intra-articular, and intramuscular)
- Review head trauma history
- Post-partum—Sheehan's (absence of lactation, menses)
- Isolated ACTH deficiency

Tumors resulting in 2˚ adrenal insufficiency

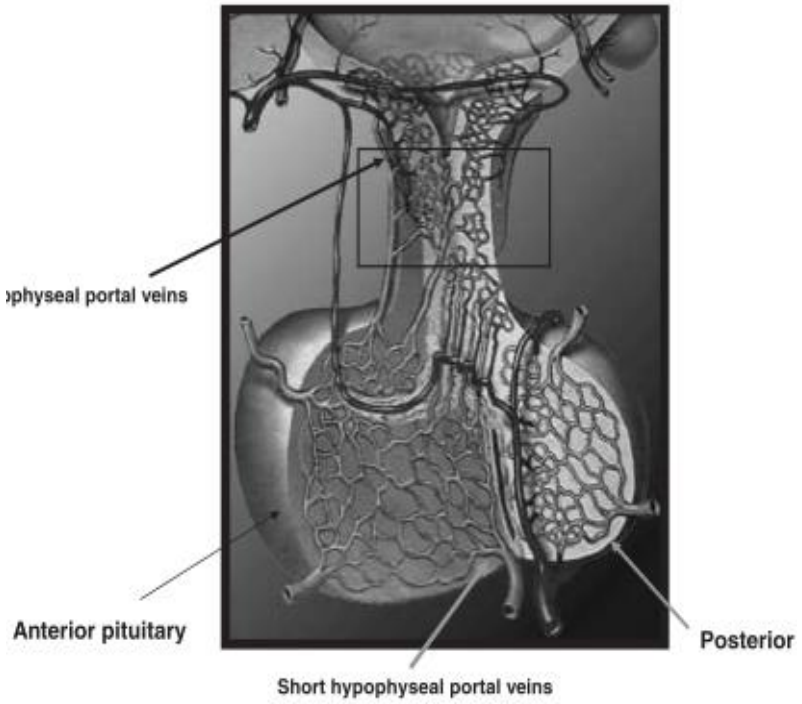
- Space-occupying lesions cause hypopituitarism by destroying the pituitary gland or by disrupting the hypothalamic-hypophyseal portal venous system
    - Pituitary adenomas
    - Other CNS tumors (meningioma, epidermoid tumors)
    - Metastases (breast cancer)

Traumatic brain injury

- Prevalence of hypopituitarism
  - up to 68.5%
- Mechanisms

  - compression of the pituitary gland and/or hypothalamic nuclei due to edema

  - direct mechanical injury to the hypothalamus, pituitary stalk (hypophysial vessels, portal capillaries) or the gland
- Growth hormone deficiency – most common pituitary deficit



Analysis of Laboratory tests in a 50-year-old woman who presents with features of adrenal insufficiency shows normal serum levels of sodium, potassium, and low cortisol levels.

What is the most likely diagnosis?

A. Addison disease
B. Adrenal metastasis from a small cell lung cancer
C. Tuberculosis of the pituitary gland
D. Congenital adrenal Hyperplasia

Infiltrative disease resulting in 2° adrenal insufficiency

- Langerhan's histiocytosis
  - Infiltration of multiple organs by well-differentiated histiocytes
  - Diabetes insipidus, anterior pituitary hormone deficiency
- Sarcoidosis
  - Multisystem granulomatous disorder characterized by the presence of noncaseating granulomas in involved organs
  - Diabetes insipidus, anterior pituitary hormone deficiency

Infiltrative disease resulting in 2˚ adrenal insufficiency

- Hemochromatosis
  - Excessive iron deposition in the tissues
  - Hypogonadotropic hypogonadism
  - Deficiency of TSH, GH and ACTH later in the course of disease

A 25-year-old lady complains of fatigue and body aching. She has lost her appetite and has nausea for the last week. You check a morning total cortisol level and find it is 4ug/dL. She is on no medications.

What is the next best step?

a. Repeat AM cortisol
b. Perform ACTH stim test
c. Start steroid replacement
d. Measure ACTH level

Diagnostic Testing- Basal Serum Cortisol

- Can be used alone to **exclude** all forms of AI in MOST patients
- Cortisol has strong diurnal rhythm
- AM cortisol before 9:00 am is diagnostically useful
- Basal cortisol values < 3 ug/dl highly suggestive but not always diagnostic (clinical correlation needed)
- BUT if cortisol drawn at any time of day is > 10 ug/dl is 99% specific for predicting a cortisol increase greater than 18 ug/dl during an ACTH stim test
- Basal cortisol values 3-10 ug/dl are inconclusive and require additional testing (ACTH STIM TEST)

Laboratory Assessment of AI

Less Useful

24 hour UFC

Serum cortisol

Corticotropin releasing

-hormone (CRH) test

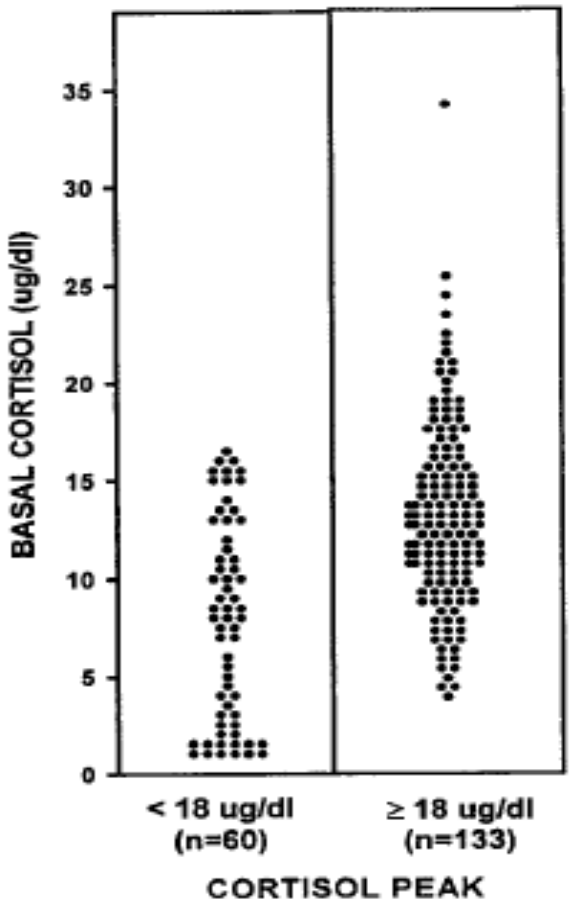
More Useful

Cosyntropin stimulation test

Metyrapone test

Insulin tolerance test

Fig. 1 Basal cortisol vs. ITT



Erturk E et al. JCEM 1998

Caveats to AI testing
True or False

- Serum AM cortisol levels are accurate even if a patient has taken a hydrocortisone or prednisone dose that morning
- Cortisol binding globulin is not affected by hyperthyroidism
- Cortisol binding globulin is increased in nephrotic syndrome

Diagnostic Testing- ACTH

- AM ACTH value itself not used to excluded adequate cortisol production
- If cortisol is low < 5ug/dl the ACTH is useful to distinguish etiology of AI
  - Primary AI: ACTH > 100 pg/ml
  - Secondary AI: ACTH < 5 pg/ml (or inappropriately low)

Serum Aldosterone & **Plasma Renin Activity**

- Not deficient in secondary AI
- Only deficient in primary AI
- Aldosterone will be low or undetectable in primary AI but only interpretable with an appropriately elevated renin (>2 ng.ml/h)

250 ug Cosyntropin Stimulation Test

- Indication: Definitively exclude primary adrenal insufficiency or *longstanding* secondary adrenal insufficiency (>3 weeks)
- Protocol: IV or IM bolus with sampling baseline, 30 min and 60 min
- Can be done ANYTIME OF DAY
- NORMAL: A peak cortisol at 30-60min of greater than 18 ug/dl
- Basal cortisol values vary by time of day and clinical status and should never be used as a diagnostic criterion
- Aldosterone normally doubles in response to cosyntropin which can be helpful

Sensitivity of Cosyntropin Stimulation Test

Keep in mind that sensitivity of cosyntropin stimulation test is 64%: *do not exclude adrenal insufficiency in patient with low cortisol, low ACTH and low DHEAS*

$$\textbf{Sensitivity} = \frac{True\ Positives}{True\ Positives + False\ Negatives}$$

$$\textbf{Specificity} = \frac{True\ Negatives}{True\ Negatives + False\ Positives}$$

$$\textbf{False Negative Rate} = \frac{False\ Negative}{True\ Positives + False\ Negatives}$$

$$\textbf{False Positive Rate} = \frac{False\ Positives}{True\ Negatives + False\ Positives}$$

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

Other dynamic testing- recommend endocrine involvement

- Insulin Tolerance Test
  - GOLD STANDARD TEST for all forms of AI
  - Tests the entire HPA axis
  - Measures the counter regulatory hormone response to hypoglycemia
  - Useful in equivocal cases of other dynamic testing & secondary AI
  - Contraindications to test: seizure disorders, significant cardiovascular disease, inability to verbalize symptoms of hypoglycemia

DHEA-S Level And DHEA-S Ratio

- Age and gender specific DHEA-S level can be measured
- DHEA-S ratio calculated by measured DHEA-S divided by the lower limit of the respective reference range for all participants.
- A DHEA-S ratio of more than 1.78 had 100% sensitivity regarding intact HPA function.

Format: Abstract Send to

J Clin Transl Endocrinol. 2017 Jan 31;7:42-46. doi: 10.1016/j.jcte.2017.01.001. eCollection 2017 Mar.

Serum dehydroepiandrosterone sulfate in assessing the integrity of the hypothalamic-pituitary-adrenal axis.

Charoensri S[1], Chailurkit L[1], Muntham D[2], Bunnag P[1].

Author information

Abstract

OBJECTIVE: To evaluate the relationship between age- and gender-adjusted dehydroepiandrosterone sulfate (DHEA-S) levels and low-dose adrenocorticotropic hormone (ACTH) stimulation in assessing the integrity of the hypothalamic-pituitary-adrenal (HPA) axis, in patients who were at risk of HPA insufficiency, including those currently being treated with glucocorticoids.

METHODS: Forty-six participants with a suspicion of secondary adrenal insufficiency were recruited from the Diabetes and Endocrinology Clinic at Ramathibodi Hospital, Mahidol University, Bangkok. Low-dose (1 μg) ACTH stimulation was performed in every participants, and serum DHEA-S was measured at baseline before ACTH injection.

RESULTS: Individuals with normal age- and gender-specific DHEA-S levels had baseline serum cortisol and peak cortisol levels higher than those with reduced DHEA-S. Normal age- and gender-specific DHEA-S levels predicted intact HPA function with a sensitivity of 87.1%, a specificity of 86.7%, a positive predictive value of 93.1%, and a negative predictive value of 76.5%. To account for the age and gender dependency of DHEA-S, the DHEA-S ratio was calculated by measured DHEA-S divided by the lower limit of the respective reference range for all participants. A DHEA-S ratio of more than 1.78 had 100% sensitivity regarding intact HPA function. Area under the receiver operating characteristic [ROC] curve was 0.920. (95% CI, 0.844-0.997).

CONCLUSION: Normal age- and gender-specific DHEA-S level or a DHEA-S ratio of more than 1.78 are valuable markers of HPA integrity. Serum DHEA-S may be a candidate for a less costly approach where ACTH stimulation is unavailable.

Other diagnosis

- Adrenal Fatigue: Doesn’t exist
- Relative Adrenal Insufficiency: according to endocrinologist doesn’t exist, possibly exists in critical care literature
  - Circulating cortisol is about 10% free hormone and 90% bound
  - The affinity of cortisol for the GC receptor is about .362 ug/dl
  - So a total serum cortisol of 7 ug/dl is about .7 ug/dl free cortisol which is nearly enough to saturate the GC receptor.
  - So during stress even “low” amounts is often enough

A female presents with anorexia, weight loss, hyperpigmentation, bowel changes, and lightheadedness on standing. The cosyntropin stimulation test shows random serum cortisol of 11 micrograms/dL. Serum cortisol 1 hour after 0.25 mg cosyntropin N is 14 micrograms/dL. Renin level is 10.

Which of the following is an appropriate treatment for this patient?

A. Hydrocortisone 15 and 5 mg mg daily for life
B. Prednisone 5 mg daily for life
C. Hydrocortisone 15 and 5 mg and fludrocortisone 0.1 mg daily for life
D. Dexamethasone 0.5 mg daily for life
E. Dexamethasone 4 mg daily and fludrocortisone 0.1 mg daily for life

Glucocorticoid Replacement Therapy

- Starting dose:
  - Hydrocortisone 15-20 mg daily in divided in 2 doses
- 10–12 mg/m^2/day
- BSA calculator: http://www.halls.md/body-surface-area/bsa.htm
- Goal of therapy:
  - Balancing physiological circadian glucocorticoid replacement against personal circumstances
- Monitoring:
  - Weight, energy level, sleep quality, use of stress dose steroids, hospital admissions, circumstances around adrenal crises
  - No bloodwork is needed for monitoring of therapy
- Take into account comorbidities that can decrease the dose of GC replacement

Signs of suboptimal replacement:	Signs of excessive replacement:
Fatigue Nausea Weight loss Adrenal crisis	Fatigue Weight gain Development of Cushingoid features Decrease in bone density

Steroid Medications

Name	Biol ½ life (h)**	Gluco-Corticoid Potency	Mineralo-Corticoid Activity
Hydrocortisone (HC)	**8-12**	**1**	**2**
Cortisone acetate	8-12	0.8	2
Prednisone	**18-36**	**4**	**1**
Prednisolone	18-36	4	1
Dexamethasone	**36-54**	**25-50**	**0**
Fludrocortisone	18-36	15	150

** different than elimination half lives

HC 20 mg (approximately) = Prednisone 5 mg
HC20 mg (approximately) = Dexamethasone 0.25 – 0.5 mg
HC 20 mg (approximate MC activity) = Fludrocortisone 50 mcg

Circardian Rhythm

- Cortisol concentrations demonstrate a circadian rhythm, controlled by the central clock situated in the hypothalamic suprachiasmatic nucleus.
- A general principle in endocrinology is to replace hormones to replicate physiological concentrations; however, the pharmacokinetics of oral immediate-release hydrocortisone make it impossible to fully mimic the cortisol rhythm and patients still have an increased morbidity and mortality despite replacement.

CLINICAL ENDOCRINOLOGY

Clinical Question | Free Access

What is the best approach to tailoring hydrocortisone dose to meet patient needs in 2012?

Miguel Debono, Richard J. Ross

First published:29 November 2012 | https://doi.org/10.1111/cen.12117 | Citations: 10

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Summary

Cortisol is an essential stress hormone and replacement with oral hydrocortisone is lifesaving in patients with adrenal insufficiency. Cortisol has a diurnal rhythm regulated by the central body clock and this rhythm is a metabolic signal for peripheral tissue clocks. Loss of cortisol rhythmicity is associated with fatigue, depression and insulin resistance. A general principle in endocrinology is to replace hormones to replicate physiological concentrations; however, the pharmacokinetics of oral immediate-release hydrocortisone make it impossible to fully mimic the cortisol rhythm and patients still

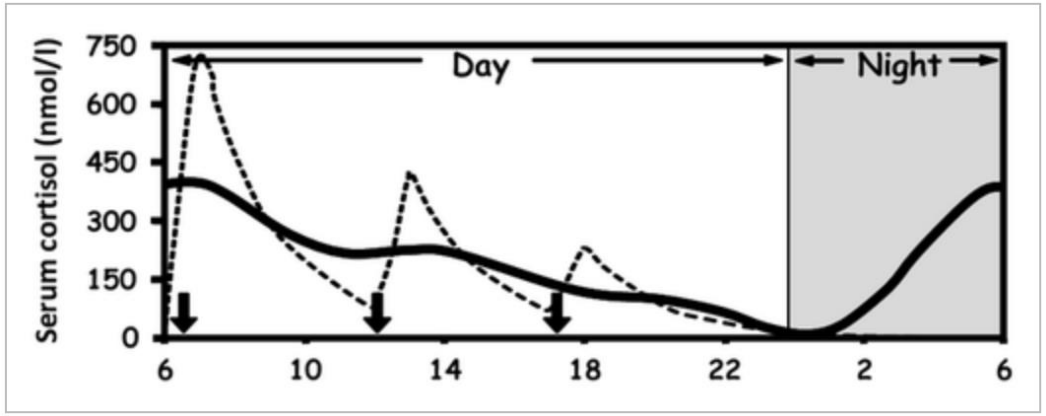
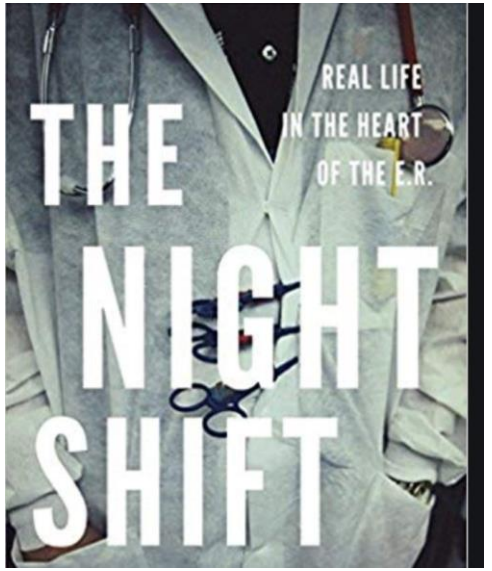


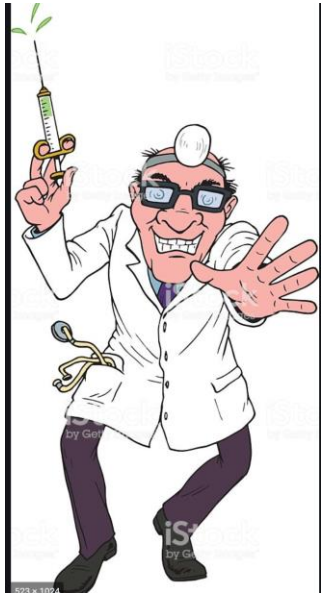
Figure 1 Open in figure viewer | PowerPoint

Circadian rhythm of serum cortisol in normal subjects (solid line) and simulated cortisol profile for a patient (broken line) following thrice-daily hydrocortisone administration (10 mg at 06:00 h, 5 mg at 12:00 h and 2·5 mg at 18:00 h (arrows).

Special Situations

- Shift worker or other individuals with shifted daily routine (adolescents, students)
  - Change glucocorticoid and mineralocorticoid replacement according to schedule
  - Take the larger dose of hydrocortisone on waking, the second dose 6-8 hours after the first one





Mineralocorticoid Replacement

- Starting dose:
  - Fludrocortisone 100 mcg daily (usually 50-300)
- Goal of therapy:
  - No orthostasis
  - K and Na, renin or renin plasma activity (upper limit of normal) – within normal range
- Monitoring:
  - Symptoms and orthostatic vitals each visit
  - Bloodwork – 3 months after each dose change, and then yearly

Signs of suboptimal replacement:	Signs of excessive replacement:
Lightheadedness, orthostasis Salt craving High K, high renin	Edema Hypertension Low K, low renin

Androgen Replacement(DHEA)

- Starting dose:
  - ➢DHEA 25 mg daily **in women** only and then increase 25 mg until 75 mg
  - ➢ On a 6 months trial basis
  - ➢Not effective
- Goal of therapy:
  - ➢"feeling better" = quality of life (energy, libido, mood)
  - ➢DHEAS in mid normal range (bloodwork: skip the mor
- Monitoring:
  - ➢Gage improvement in symptoms (subjective)
  - ➢ Blood-work – 3 months after each dose change, and t
- ➢Do not work in other situations

Acute Ill Management with AI

- Aggressive volume replacement with normal saline
- Use of vasocontraction medications
- If not response
  - Hydrocortisone (solu-cortef) as IV bolus or infusion, IM ok as well if no IV access
- Exact dose not critical just get some in ASAP
- 20mg HC will sufficiently raise serum cortisol concentrations

Acute Management of AI

- Presumed maximal output of hydrocortisone during severe stress is 200-300mg/day
- Doses of 50mg q6 will raise serum cortisol to 40-120mg/dl
- MOST IMPORTANT is to continue the dosing until patient is well then can take oral regimen

Acute Management of AI

- Doses of hydrocortisone greater than 40mg/dl per day also have a mineralocorticoid effect so do not need fludrocortisone replacement
- If use dexamethasone, need to give fludrocortisone
- Pts promptly respond to the first dose of hydrocortisone

Special Situation

Binding Globulins Effect on Cortisol Level

Total Cortisol

- 4-5% free “bioactive” circulating cortisol
- 80-90% - bound to corticosteroid-binding globulin (CBG)
- 5-10% - bound to albumin and erythrocytes

Increased CBG → increased total cortisol	Decreased CBG – decreased total cortisol
Pregnancy Synthetic estrogens	Sepsis, critical illness, Trauma, Major surgery Chronic liver disease, Chronic kidney disease Gene mutations in CBG
Very strong clinical suspicion of adrenal insufficiency despite normal total cortisol concentrations	

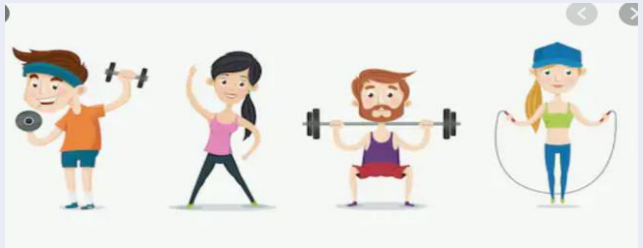
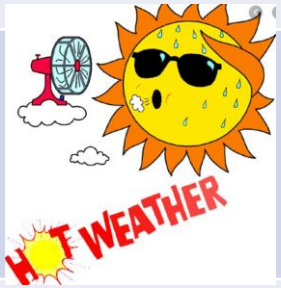
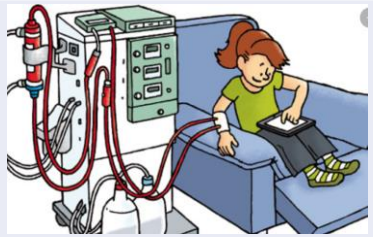
Pregnancy

- Glucocorticoids:
  - ➢ 2nd and 3rd trimester: increase in CBG, total cortisol a
  - ➢ consider an increase in hydrocortisone dose (20-40% of total daily dose)
  - ➢Avoid dexamethasone
- Mineralocorticoids:
  - ➢ consider change in min
    progesterone is anti-mir
  - ➢monitor with sodium/pc
    pregnancy and thus not

Prevention of adrenal crisis:

- Education!!!
- Supplies (Hydrocortisone vials, syringes, needles)
- Follow up and availability of quick advice to patient – phone number
- Provide stress dose replacement around delivery (100 mg at onset of labour, then 200 mg/24h followed by rapid tapering)

Other special situations

Situation	Action
Insulin dependent diabetes mellitus 	Consider longer-acting glucocorticoids, e.g. prednisolone to avoid cortisol-driven peaks and troughs in blood sugar
Excessive exercise 	Small carbohydrate meal before exercising Additional salt requirement to replace sweat losses, consider small dose increases in glucocorticoid and mineralocorticoids when undertaking extraordinarily strenuous exercise (e.g. consider 2.5-5mg hydrocortisone every 3 hours during a marathon
Hot environment 	Additional salt requirement to replace sweat losses Consider increase fludrocortisone by 50-100µg per day to compensate for salt and water loss
Dialysis 	Stop fludrocortisone (no longer needed). Plan glucocorticoid replacement (substantial amounts of the morning glucocorticoid dose might be lost through hemodialysis)

What About Testing In Critically ill Patients?

- The diurnal rhythm of ACTH and cortisol secretion is disrupted in acute illness
- Patients who are hemodynamically unstable, unresponsive to vasopressors, with signs and symptoms suggestive of AI → should be treated with stress dose steroids
- Controversy regarding testing given concerns of the existence of cortisol resistant state in critically ill individuals caused by inflammatory cytokines, a reduction in CBG and proin[illegible]mato[illegible]nscription factors

Dynamic pituitary-adrenal interactions in the critically ill after cardiac surgery

Ben Gibbison MD FRCA FFICM[1*], Daniel M Keenan PhD[2], Ferdinand Roelfsema MD PhD[3], Jon Evans BSc[4], Kirsty Phillips BSc[5], Chris A Rogers PhD[4], Gianni D Angelini MD FRCS FECTS[6], Stafford L Lightman PhD FRCP FMedSci FRS[7]

This study is clinically relevant because it is very common to test serum cortisol or to perform an ACTH stimulation test in critically ill patients before starting steroid replacement. The evidence that emerges from this study makes us realize that this practice is inappropriate due to the poor understanding of the HPA axis in this type of subject.

Expert Critique

FROM THE ENDOCRINE SOCIETY READING ROOM

Ricardo Correa, MD, Es.D, FACP, FACE, CMQ
Program Director, Endocrinology, Diabetes and Metabolism
The University of Arizona, College of Medicine-Phoenix
Phoenix, AZ

Adrenal insufficiency (AI) in the critically ill patient is a relevant topic that affects morbidity and mortality. It is well known that this population is at higher risk to develop AI.

Asked to see pt regarding diagnosis of adrenal fatigue in 19 y/o man complaining of panic attacks accompanied by palpitations and weakness.

Diagnosis of adrenal fatigue made by a salivary cortisol profile.

Pt's mother at the visit

Normal skin pigmentation

124/74 HR 60

BMI 21

PE=normal

Early morning cortisol 1.2 ug/dl

Which of the following testswould you obtain next?

A. Plasma ACTH

B. 250 ug ACTH stimulation test

C. Pitultary MRI

D. DHEA-S

250 ug Stim test was done and peak cortisol was 11.6 ug/dl
Basal ACTH < 5
Total T, Free T4, IGF-1 wnl

Which of the following studies would you get next?

A. Pituitary MRI
B. ITT
C. 1 ug cosyntropin stimulation test
D. Renin level

Pituitary MRI is normal

Which of the following studies would you get next?

A. Measurement of long chain fatty acids

B. 21 Hydroxylase antibodies

C. Synthetic glucocorticoid screen

D. 17 Hydroxyprogestone (Congenital Adrenal hyperplasia)

Synthetic GC screen negative

Two weeks later the initial visit, the patient's mother calls you and finds what in his drawer?

Opioid

1. Does he really have adrenal insufficiency?
2. Should you treat?

Thanks…Questions??

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