

Outline

Adrenal Insufficiency

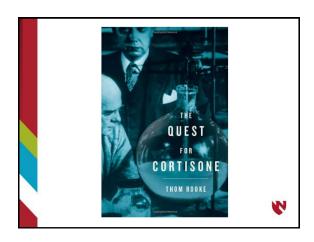
- · Potential causes
- · Who to screen
- · Labs what to check and when
- · Interpreting results
- Treatment
- · Exogenous Steroids

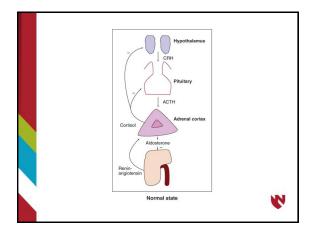
Adrenal Fatigue

- · Evidence against
- · Talking points with patients









Primary vs Secondary

1° → Problem **inside** adrenals

- Destruction of adrenal cortex:
 ↓ cortisol & MCs
 - Addison's disease
 - Infectious, TB
 - Malignant
 - Hemorrhage
 Opportunistic infections
 - Drugs
- $2^{\circ} \rightarrow$ problem **outside** adrenals
- Pituitary/hypothalamic insufficiency
 - Tumors
 - Radiation
 - Trauma
 - Hemorrhage
 - Inflammation
 - Granuloma
 - Sheehan's syndrome

Exogenous steroids: suppress CRH/ACTH atrophy of adrenal glands with long term usage



Other drugs causing Al

Inhibition of cortisol synthesis:

- Etomidate, ketoconazole, fluconazole, metyrapone
- Al may develop if limited pituitary/adrenal reserve usually not with normal HPA axis

Acceleration of metabolism of cortisol and most synthetic GCs

- · Phenytoin, barbituates, rifampin
- · Al seen if limited pituitary/adrenal reserve and those with Al on GC therapy

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· Risk of bilateral adrenal hemorrhage that can cause Al

Ipilimumab

- CTLA-4 antibody used for advanced melanoma
- A/w secondary AI, hypogonadism, and hypothyroidism; Primary AI also described

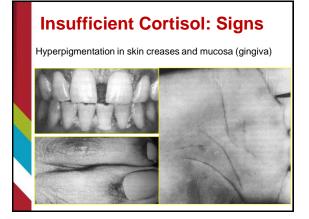


- Glucocorticoids
- Megace
 - High dose progestin with some GC activity via binding to GC recentor.
 - · Increases appetite with cancer anorexia/cachexia, AIDS wasting
 - Pts may be Cushingoid, withdrawal can occasionally cause secondary AI
- Opiates *****
 - · Chronic administration can cause secondary Al
 - · Mechanisms poorly understood
 - ~ 70% of heroin addicts have impaired cortisol response to CST
 - Primary theory → opioids act on neurotransmitters that regulate CRH → suppresses ACTH & cortisol
 - · Not clear whether and how this should be treated



Symptoms Table 1. Clinical Features of Adrenal Insufficiency and Adrenal Crisis Symptoms Signs Feats Adrenal Insufficiency Fatgue Hyperpigmentation (primary only), particularly of sun-exposed areas, skin creases, mucosal membranes, scars, area of of Postural dizzines Postural dizzines Postural dizzines Postural dizzines Postural dizzines Postural dizzines Failure to trivire in children Adrenal crisis Symcope Abdominal pain, nausea, vomiting: Abdominal tendernes/guarding mity minic acute abdome Reduced consciousness, delirium Not very sensitive or specific Consider with unintentional weight loss, hypotension, or unexplained hyponatremia (sep if a/w hyperkalemia) In absence of concomitant conditions like renal/heart/liver failure, weight gain essentially excludes diagnosis of Al





Diagnosis

Challenging - often insidious onset of nonspecific sx over months – years

Keep the threshold for diagnostic evaluation low

Consider starting with 8AM cortisol

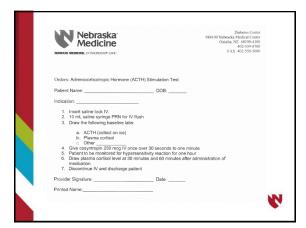
- > 14 → very unlikely
- < 5 suggestive of AI
- AM cortisol values 5-14 g/dL → inconclusive, require additional testing
- ACTH used to distinguish primary v secondary when AM cortisol is < 5



ACTH Stim Test

- · 250mcg cosyntropin
- Can definitively exclude primary AI or longstanding secondary AI
- · Cortisol at 30 or 60 minutes > 18 is normal
- · Do not use change in cortisol as diagnostic criteria -
 - Highly dependent on the basal value, which varies by time of day and clinical status
- Check ACTH with baseline cortisol during stim or with an AM cortisol





Diagnosis, cont.

Severe AI sx or adrenal crisis \rightarrow unstable, unresponsive to fluids/pressors

- · Draw blood for random cortisol, ACTH no stim test
- Immediate tx with stress dose IV hydrocortisone don't wait for labs!



Insulin Tolerance Test

- · Gold standard
- Primarily used for suspected secondary AI and equivocal basal testing
- Give IV bolus of regular, draw cortisol levels q 15 min x 75 min
- · Need glc < 40 to interpret an abnormal test
- Normal cortisol responses is > 18 g/dL
- Contraindicated in seizure disorders, significant CVD, inability to verbalize symptoms of hypoglycemia
- · Can also eval growth hormone deficiency



Other tests

AM salivary cortisol:

- > 16 nmol/L essentially excludes AI
- < 5 → High probability of AI
 - Has only been used for screening not fully validated as the only diagnostic test
 - Patients in whom the clinical suspicion is higher or who have low or intermediate values require additional testing

Afternoon/evening serum cortisol measurements -

- At 4 PM, normal serum cortisol ranges from 3 to 10 mcg/dL
- Cortisol is lowest (<5) one hour after usual time of sleep (circadian rhythm in ACTH secretion)
- Of no value in establishing AI dx



Other things to consider

Plasma cortisol 80% bound to CBG, 10 -15% to albumin, 5-10% free

Disorders that reduce (rare genetic disorders) or increase CBG levels (estrogen, pregnancy) need to be considered when interpreting plasma cortisol

Exogenous estrogen (OCPs) → increased CBG → falsely increased cortisol levels – free cortisol levels preferred

Hypoproteinemia

- ↓ plasma cortisol binding, ↑ free cortisol fraction
- In critically ill patients with albumin < 2.5, cosyntropin stimulated total cortisol values as low as 7 can be normal – need free cortisol levels

Higher level of suspicion warranted in patients with compatible sx with autoimmune disorders or on relevant meds



Diagnosis

- Primary AI → ACTH usually 2x ULN
 - · Check 21-hydroxylase antibody
 - · Consider adrenal imaging
- Secondary → ACTH low or normal
 - Broader pituitary eval to look for other abnormalities
 - · Consider MRI pituitary
 - · Review possible offending meds
 - · Replace cortisol prior to thyroid hormone



Treatment

Hydrocortisone (15-25 mg) in 2-3 divided PO doses/day preferred

- Most physiologic, least likely to cause iatrogenic Cushing's
- · Partial secondary Al may require less
- Prednisone not preferred metabolized to active prednisolone in the liver, which is unpredictable at the smaller doses for Al
- Dexamethasone not advised risk of Cushingoid sx, harder to titrate
- · Sustained release preparations available in Europe
- Highest dose in AM at awakening, the next either in the early PM (2 dose regimen) or lunch and PM (3-dose regimen).
- · Later doses can cause insomnia

Labs not suggested to adjust treatment - only clinical response



agnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. JCEM 20

Response to GC Therapy

- · Use general clinical signs to assess adequacy of replacement
- Adequate tx should improve weakness, fatigue, anorexia, GI sx
- · Weight should return to normal
- · Hyperpigmentation improves, may not disappear
- Ideal dose → lowest amount needed to provide sense of well-being
- · Urine free cortisol not helpful
- ACTH not helpful often remains high although low/normal or low suggests over-replacement
- Signs of Cushing's → overtreatment!
 - Supraclavicular fat pads, easy bruising, facial plethora, hyperglycemia
 - · Risk of increased bone loss, osteoporosis



Additional Considerations with Primary Al

Mineralocorticoid Replacement

- Indicated if aldosterone deficiency confirmed (90%)
- Fludrocortisone taken qAM 0.05 0.2 mg/day
- Monitor dose with clinical assessment (salt craving, postural hypotension, or edema), and electrolytes
- Adequate replacement → normal BP without orthostasis, normal Na and K
- Overtreatment → HTN, low K



Additional Considerations with Primary Al

DHEA

- Consider 6 mo trial in women with low libido, depressive sx, and/or low energy levels despite optimized GC and MC tx
- · Aim for mid-normal AM DHEA levels

Periodic screening for autoimmune diseases

- · Optimal frequency of screening unknown
- Thyroid disease, DM, premature ovarian insufficiency, celiac disease, and autoimmune gastritis with B12 deficiency



Stress Dosing/Patient Education

- Educate about adjusting meds during stress
- Home management of illness with fever:
 - Double (>38°C) or triple (>39°C) until recovery (usually 2-3 days)
 - · Increase electrolyte-containing fluids as tolerated
- If unable to tolerate PO need home IM or IV GC replacement
 - All need a GC injection kit
- · Steroid emergency card
- · Medical alert ID



Stress Dosing

- Planned surgeries → 50mg IV HC, then 25mg IV q 6 until able to take PO
- · MC dosing may be suspended during high dose HC
- Dental procedures, colonoscopies, and minor surgeries < 2 hours
 - · Doubling AM oral dose preop usually sufficient
- Major surgery with general anesthesia, trauma, ICU stay → stress dose IV HC (50 IV q 6), IVF



Case #1

44 yo F with PMH pertinent for hypothyroidism

- November → hospitalized for N/V, noticed hands and face were darker
- December → lightheaded, nauseous, dizzy, could work only 1 hr
 - · Put on Topamax for migraines, anxiety meds increased
 - Skin continued to darken, including stomach and chest
 - · Lost 65 lbs in 3 months. Couldn't eat 2/2 nausea.
- · Recurrent sinusitis felt much better while on steroid bursts
- · Father with RA, pulmonary fibrosis
- Hospitalized in Jan for N/V, AKI, dehydration, hypotension
- All cortisols < 3, but dex given in ED prior to labs
- Hyponatremic, hyperkalemic
- Discharged on HC 10-5-5 due to high suspicion labs pending



Case #1, cont.

- ACTH returned > 900, 21-hydrox ab 19 (normal <1)
- HC continued. In f/u she endorsed persistent light headedness, dizzy spells, poor appetite, salt craving, nausea.
 - · Started florinef 0.1mg daily, increased to 0.2mg
 - · Increased HC dose with no improvement
- Sx improved but not back to baseline until DHEA started, 25mg daily
- Backed HC down to 10-5-5
- Back to working full days



Case #2

70 yo M presents with worsening fatigue, joint pain, lightheadedness.

AM cortisol 3.1

Denies oral, topical steroids

Later mentions he sees a provider for regular back injections for the last 4 years, although he doesn't know what is in the shots.

Usually goes every 3 months but had to miss his last appointment



Exogenous Steroids

- All exogenous glucocorticoids, regardless of dose and route, can suppress HPA axis
- Endogenous cortisol deficiency occurs in 50% receiving intra-articular or oral GCs
 - May even be present in 5–10% of patients on inhaled or topical steroids
- HPA axis suppression occurs with doses of prednisone > 5mg/day
- · Degree of suppression varies, hard to predict
- Severity of side-effects usually relates to dose and duration of therapy, but there is marked individual variation



Greenspan's Basic & Clinical Endocrinology
Endo Society 2016 Meet the Professor. Adrenal Insufficiency, Subclinical and Adrenal Fatigu

Exogenous Steroids

- Assume clinically significant axis suppression if:
 - Clinical sx of Cushing's
 - Receiving 10-20mg of pred/day x > 3 weeks
- Even after doses have been decreased to physiologic levels, axis suppression persists average of 9-10 months, may continue for 1-2 years
- Taper steroids as the clinical situation permits no clear guidelines available
- Disease recurrence may limit ability to taper
- Steroid withdrawal syndrome can present with fatigue, arthralgias
- Psychologic dependence has also been described
- Arthritis remedies purchased online may have various synthetic corticosteroids
- Synthetic glucocorticoid screen (Mayo) if suspect Al from exogenous steroids



Case #3

63 yo M with Churg Strauss, dx 2013. On Azathioprine and prednisone since dx, prednisone doses ranged 5-30mg daily. 5 mg daily was typical. Stopped completely in March 2017, rheum hoping to manage him with rituxan alone. Shortly experienced worsening fatigue, joint pain, eczema. Prednisone restarted, sx resolved.

Options

- · Taper pred slowly by 1mg/month, or as tolerated
- Transition to HC equivalent in divided doses, taper based on 8AM cortisol after skipping PM dose

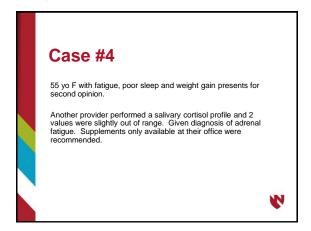


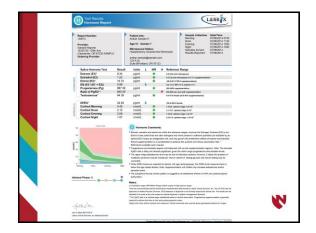
Assessing underlying axis

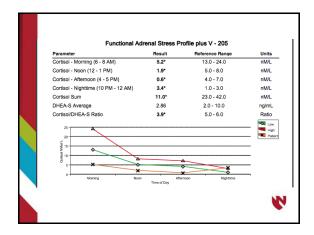
- HC 100% reflected in cortisol assay
- Dex 0%
- · Prednisone 10-20%
- · Switch to equivalent dose of HC (2-3x/day)
- · Hold PM dose
- · Check 8AM cortisol
- If > 10, continue to taper HC

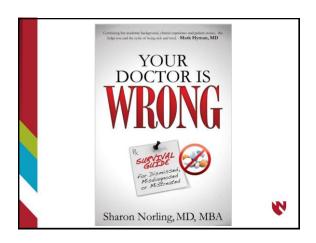


Equivalent Dose	Sterold
1.2 mg	Betamethasone (long-acting)
1.5 mg	Dexamethasone (long-acting)
8 mg	Methylprednisolone (intermediate-acting
8 mg	Triamcinolone (intermediate-acting)
10 mg	Prednisone (intermediate-acting)
10 mg	Prednisolone (intermediate-acting)
40 mg	Hydrocortisone (short-acting)
50 mg	Cortisone (short-acting)









Adrenal Fatigue

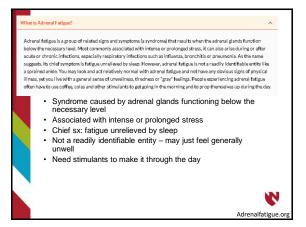
- Website of chiropractor and naturopath James L. Wilson, DC, ND, PhD, says he coined the term adrenal fatigue in 1998 "to identify below optimal adrenal function resulting from stress and distinguish it from Addison's disease."
- Website notes that "conventional medicine does not yet recognize it as a distinct syndrome."

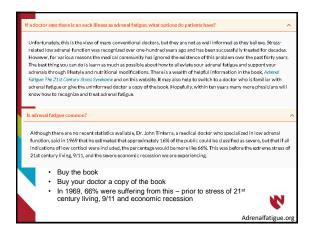


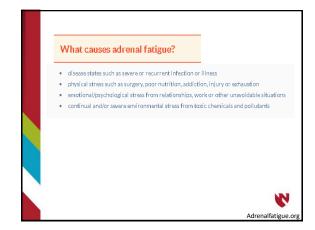


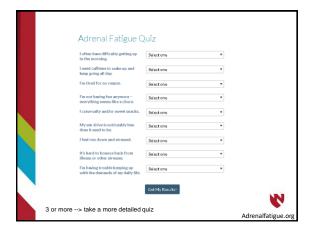


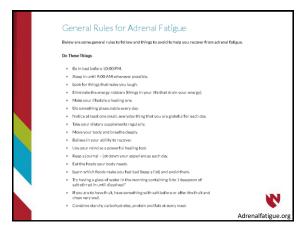


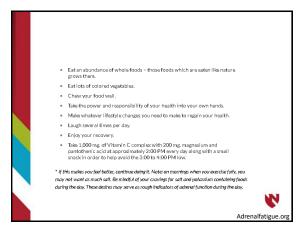




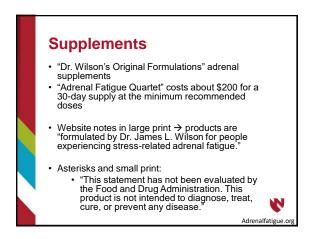








Avoid These Things Getting overtired Caffeine, sugar, alcohol, and white flour products Coffee, even decaf Staying up past 11:00 PM Pushing yourself Energy suckers (people, places and things that make you feel worse or discourage your recovery) Being harsh or negative with yourself · Feeling sorry for yourself · Foods you are addicted to · Foods you suspect an allergy or sensitive to . Foods that make you feel worse, cloud your thinking or pull you down in Never skip breakfast. · Avoid fruit in the morning. Never eat starchy carbohydrates (breads, pastas) by themselves. Do not eat foods that adversely affect you in any way, no matter how good they taste or how much you crave them. Adrenalfatigue.org



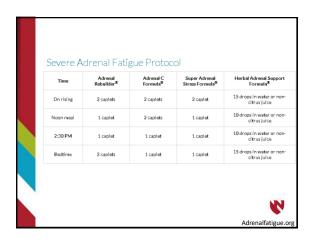




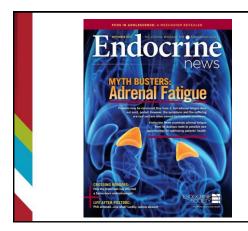














Adrenal Fatigue

- Concept promoted by integrative and naturopathic medicine based on salivary cortisol day curves
- Reference ranges are arbitrary, very narrow most have at least one measurement outside the "normal" range
- Patients often provided with "adrenal support," some actually given glucocorticoids based on salivary cortisol day curve results
- · Few, if any, have any biochemical evidence of cortisol deficiency
- Premise → constant stress puts undue burden on the adrenal glands to produce hormones — especially cortisol — and the glands burn out
- Leads to fatigue and need for stimulants to get through the day



Endo Society 2016 Meet the Professor. Adrenal Insufficiency, Subclinical and Adrenal Fatigu
The Myth of Adrenal Fatigue. Endocrine News, Sept 201

Adrenal Fatigue

- With many people feeling stressed and sleep-deprived, the appeal
 of this diagnosis is that it promises an explanation and treatment
 for fatigue
- No scientific evidence to support the existence of adrenal fatigue
- The idea that chronic stress physical or psychological may down regulate the HPA axis is not supported by any good clinical science
- Under stress, adrenals work harder and make more cortisol, not less



Endo Society 2016 Meet the Professor. Adrenal Insufficiency, Subclinical and Adrenal Fatigue. Endocrine News, Sept 201:

Adrenal Fatigue

- Literature review published last year in BMC Endocrine Disorders found "no substantiation that 'adrenal fatigue' is an actual medical condition. Therefore, adrenal fatigue is still a mvth."
- · Not recognized by any endocrinology society
- Patients with chronic fatigue syndrome have not been shown to have any consistent dysregulation of pituitaryadrenal function
- Well-designed RCTs assessing the use of hydrocortisone in CFS have shown only short-term benefit



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Adrenal Fatigue

- Reported symptoms of adrenal fatigue do not match those of adrenal insufficiency, although there is some overlap.
- · Adrenal fatigue symptoms are mostly nonspecific:
 - Feeling tired or fatigued to the point of having trouble getting out of bed
 - · Poor sleep
 - · Feeling anxious, nervous, or rundown
 - · Craving salty and sweet snacks
- · Whereas sx of chronic adrenal insufficiency include:
 - Weight loss
 - · Joint pain
 - · Anorexia, N/V, diarrhea
 - Low BP
 - · Fatique



The Myth of Adrenal Fatigue. Endocrine News, Sept 2017

Adrenal Fatigue

- When patients present claiming that stress has worn out their adrenals, it can be easy to discount their belief in "adrenal fatigue," but they often have real symptoms that require treatment
- · Reported symptoms should be taken seriously
- Explain that while you are open to complementary medicine, the adrenal fatigue explanation does not fit your understanding of how the adrenal glands work and salivary tests are not considered reliable
- Take a careful history, investigate the causes of each symptom or group of symptoms
- Exclude anemia, OSA, IBS, depression or anxiety, diabetes, other systemic illness, poor diet, stress at work or home



The Myth of Adrenal Fatigue, Endocrine News, Sept 201:

Adrenal Fatigue

- ACTH stim → if normal, shows that adrenals can respond to the stimulation by releasing cortisol, and disproves theory that glands are burned out
 - Do this off supplements!!
- Dr. Neiman →
 - Generalized symptoms can be 'couch potato syndrome,' – people get deconditioned if they don't exercise.
 - 'Life is hard syndrome.' People become stressed to the point of not taking care of themselves
- Recommendations of naturopaths have value when they emphasize eating a healthier diet, getting enough rest, exercising, and eliminating negative things from their lives

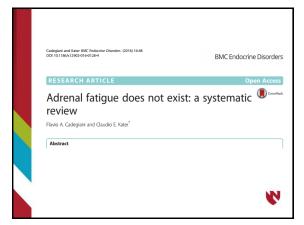


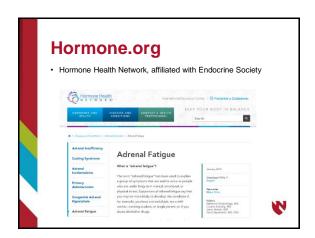
The Myth of Adrenal Fatigue. Endocrine News, Sept 2017

Adrenal Fatigue - Supplements

- Not regulated or approved by the FDA no way to know what is in them
- · Some contain ground up bovine adrenals
- · Patients should be advised to discontinue these
- Use this visit to optimize a patient's health focus on diet, exercise, sleep hygiene – which can improve these symptoms
- · Listen and validate sx
- "I really don't think your adrenals are actually failing, but I think some of your problems are reversible."







HHN pearls on adrenal fatigue

- No scientific proof exists to support adrenal fatigue as a true medical condition.
- If you are told you have this condition, the real cause of your symptoms may not be found and treated correctly.
- Treatment may be expensive; insurance companies are unlikely to cover the costs.
- If you are advised to improve your lifestyle, starting an exercise program, eating healthy foods, and following a daily routine for sleeping and waking will almost always make you feel better, no matter what the medical diagnosis.
- Supplements or vitamins sold as a treatment for adrenal fatigue could hurt you. Many of these supplements have not been tested for selection.



http://www.hormone.org/diseases-and-conditions/adrenal/adrenal-fatigue

HHN pearls on adrenal fatigue

- If you take adrenal hormone supplements when you don't need them, your adrenal glands may stop working and become unable to make the hormones you need when you are under physical stress.
- Symptoms of fatigue, weakness, or depression could indicate medical issues such as adrenal insufficiency, depression, sleep apnea, or other health problems.
- Getting a real diagnosis is very important to help you feel better and overcome your health problem.



http://www.hormone.org/diseases-and-conditions/adrenal/adrenal-fatigue

Mayo Clinic

"It's frustrating to have persistent symptoms your doctor can't readily explain. But accepting a medically unrecognized diagnosis from an unqualified practitioner could be worse. Unproven remedies for so-called adrenal fatigue may leave you feeling sicker, while the real cause — such as depression or fibromyalgia — continues to take its toll."



Conclusions

- · With the exception of axis suppression by exogenous steroids, AI is rare.
- Probability of AI is low in the absence of features like hyperpigmentation, hypotension, hypoglycemia, vitiligo, known pituitary disease, weight loss, and anorexia.
- If a diagnosis is made, the etiology needs to be pursued because this may have additional consequences
- A diagnosis of Al carries profound implications: life-long replacement therapy, medical alert identification, increased risk of death.
- Do not label someone with this diagnosis unless you are absolutely certain.
- Adrenal fatigue does not exist
- Sleeping more, eating better and exercise make everyone feel better
- It can be easy to discount beliefs in "adrenal fatigue," but patients often have real symptoms that require treatment reported symptoms should be taken seriously



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