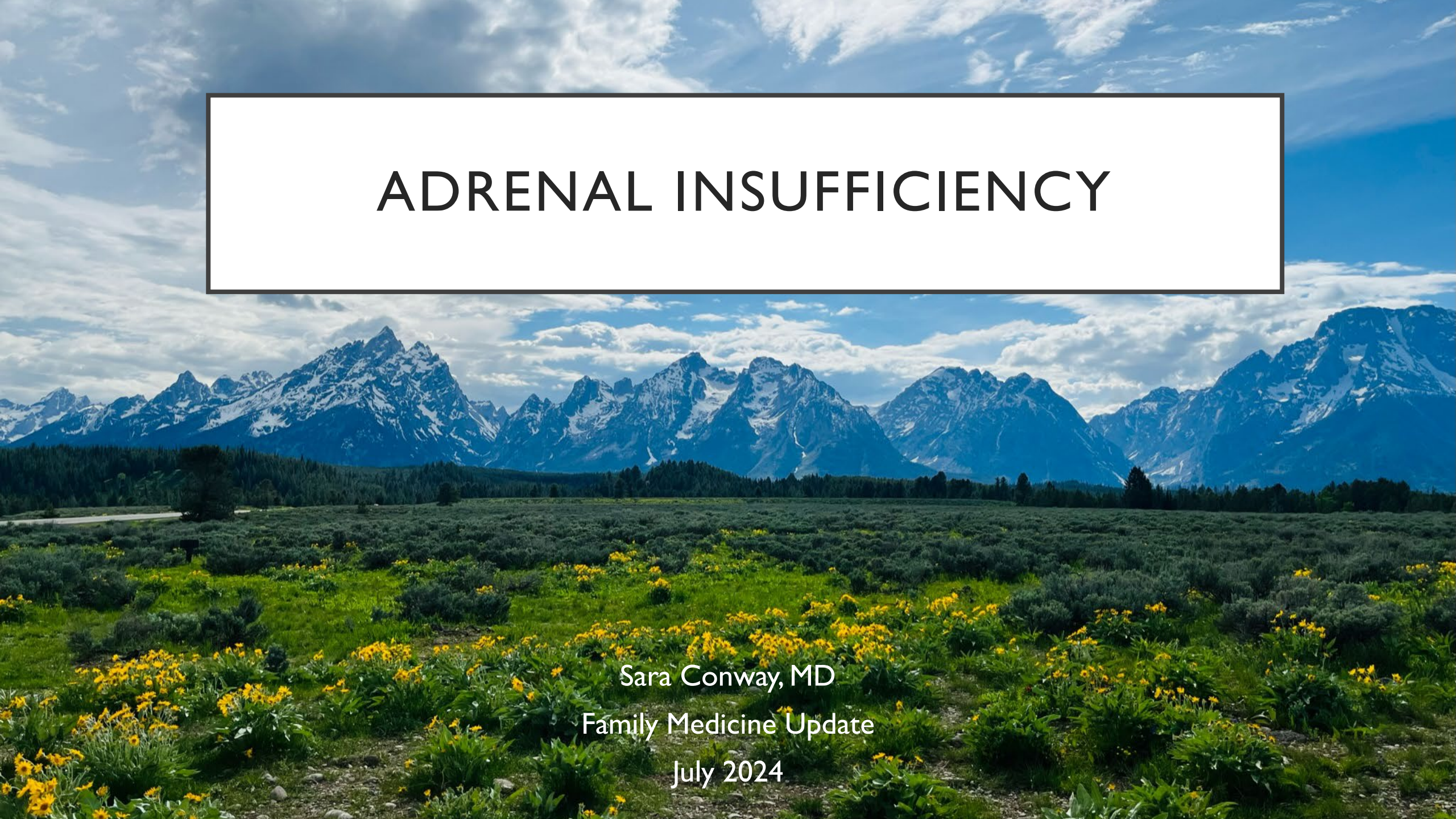

ADRENAL INSUFFICIENCY

Sara Conway, MD

Family Medicine Update

July 2024

OBJECTIVES

Review HPA axis and pathophys of adrenal insufficiency

Common signs/symptoms of AI and when to suspect

Initial work up and confirmation

Treatment

The Journal of Clinical Endocrinology & Metabolism, 2024, **00**, 1–27
https://doi.org/10.1210/clinem/dgae250
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Clinical Practice Guideline

European Society of Endocrinology and Endocrine Society Joint Clinical Guideline: Diagnosis and Therapy of Glucocorticoid-induced Adrenal Insufficiency

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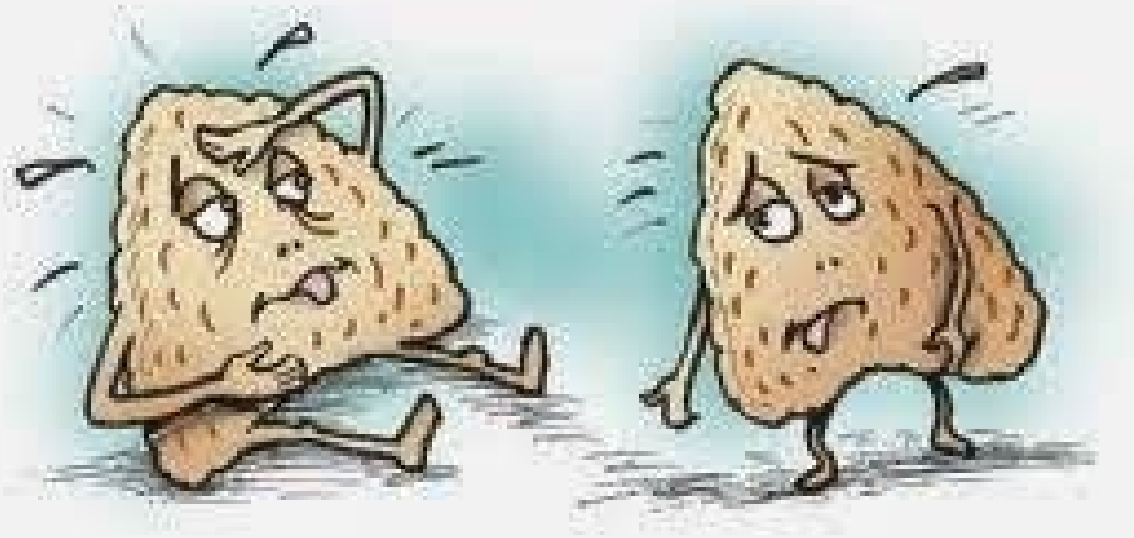
BACKGROUND

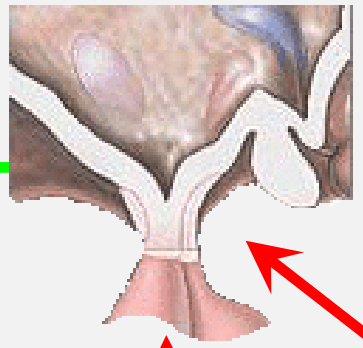
- Primary adrenal insufficiency
  - Incidence: 100-140 per million in developed countries
  - Most commonly autoimmune (80-90%)[1]
- Secondary/tertiary adrenal insufficiency
  - Incidence: 150-280 per million
    - Likely increasing due to: glucocorticoid induced AI
- Adrenal crisis is life threatening
  - Incidence 6-8/100 patients/year
  - 0.5 deaths/100 patient-years[2]
- Symptoms are non-specific and can delay diagnosis/treatment

WHAT'S THE PROBLEM?



- Inability to produce ***glucocorticoid***
  - +/-mineralocorticoid
  - +/- DHEAS

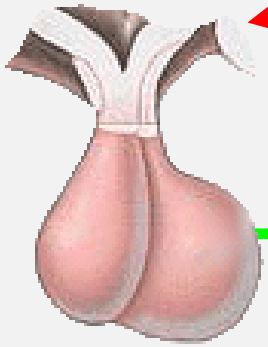
Hypothalamus



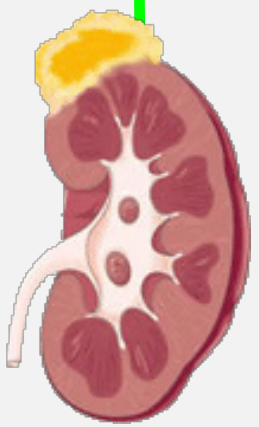
STRESS:
Physical stress
Emotional stress
Hypoglycemia
Cold exposure
Pain

CRH

CORTISOL

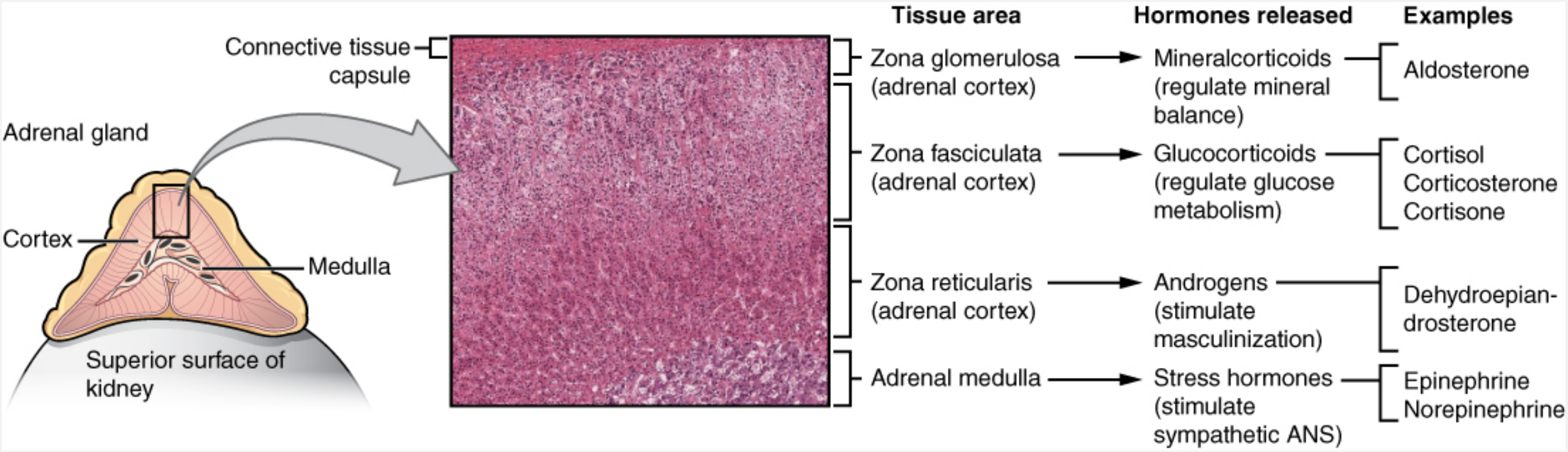


ACTH



Anterior Lobe of
Pituitary Gland

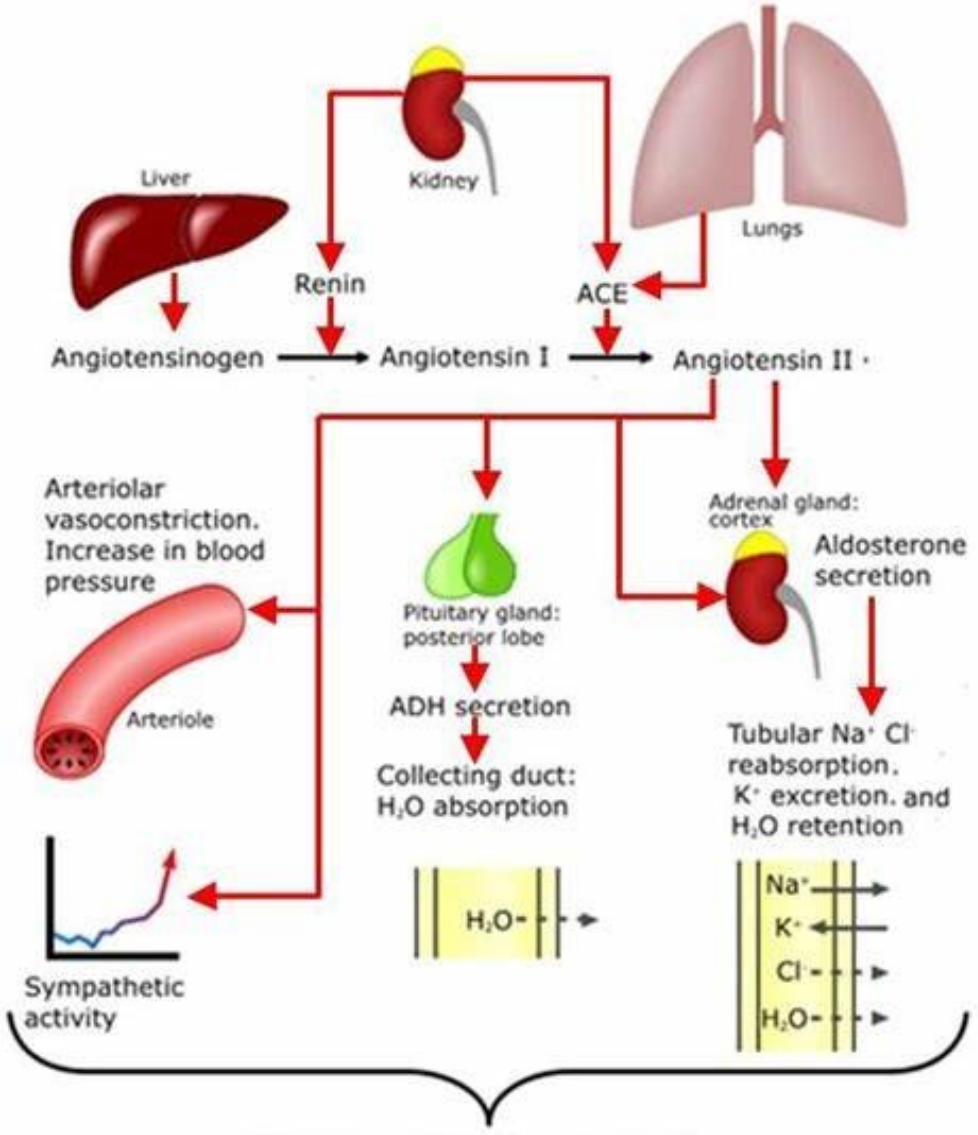
Adrenal Cortex



Functions:

- Regulate body's adaptive response to stress
- Maintenance of body water and BP
- Regulate sodium and potassium balance
- Mobilize energy stores
- Minor sex hormone production

Renin-Angiotensin-Aldosterone System (RAAS)



Water and Sodium retention.
Increased circulating volume. Increased renal perfusion.

CLINICAL

- Variable
  - Vague > Adrenal crisis
- Chronic v Acute
- Primary v Secondary

**Commonly: Fatigue, anorexia, abd pain/nausea/vomiting

Depends on rate and degree of loss of function … May go undetected until stressor precipitates crisis

Clinical manifestations of chronic adrenal insufficiency

Symptom	Frequency (%)
Weakness, tiredness, fatigue	100
Anorexia	100
Gastrointestinal symptoms	92
Nausea	86
Vomiting	75
Constipation	33
Abdominal pain	31
Diarrhea	16
Salt craving	16
Postural dizziness	12
Muscle or joint pains	6 to 13
Sign	
Weight loss	100
Hyperpigmentation	94
Hypotension (systolic BP <110 mmHg)	88 to 94
Vitiligo	10 to 20
Auricular calcification	5
Laboratory abnormality	
Electrolyte disturbances	92
Hyponatremia	88
Hyperkalemia	64
Hypercalcemia	6
Azotemia	55
Anemia	40
Eosinophilia	17

- **? Adrenal crisis** - Critically ill pt with peripheral vascular collapse whether or not the patient is known to have AI
- **Chronic adrenal insufficiency** – Patients with fatigue, weakness, myalgias, arthralgias, anorexia, and weight loss, postural hypotension, salt craving and hyperpigmentation
- **Patients on glucocorticoids for more than 3-4 weeks**

- **Disease states** T1DM, autoimmune gastritis/pernicious anemia, vitiligo, thyroid
- **Infections** TB, HIV, CMV, candidiasis, histoplasmosis
- **Meds**
  - Adrenal enzyme inhibitors: mitotane, ketoconazole, metyrapone, etomidate
  - Increase cortisol metabolism: phenytoin, ritonavir, carbamazepine, mitotane, St Johns Wort

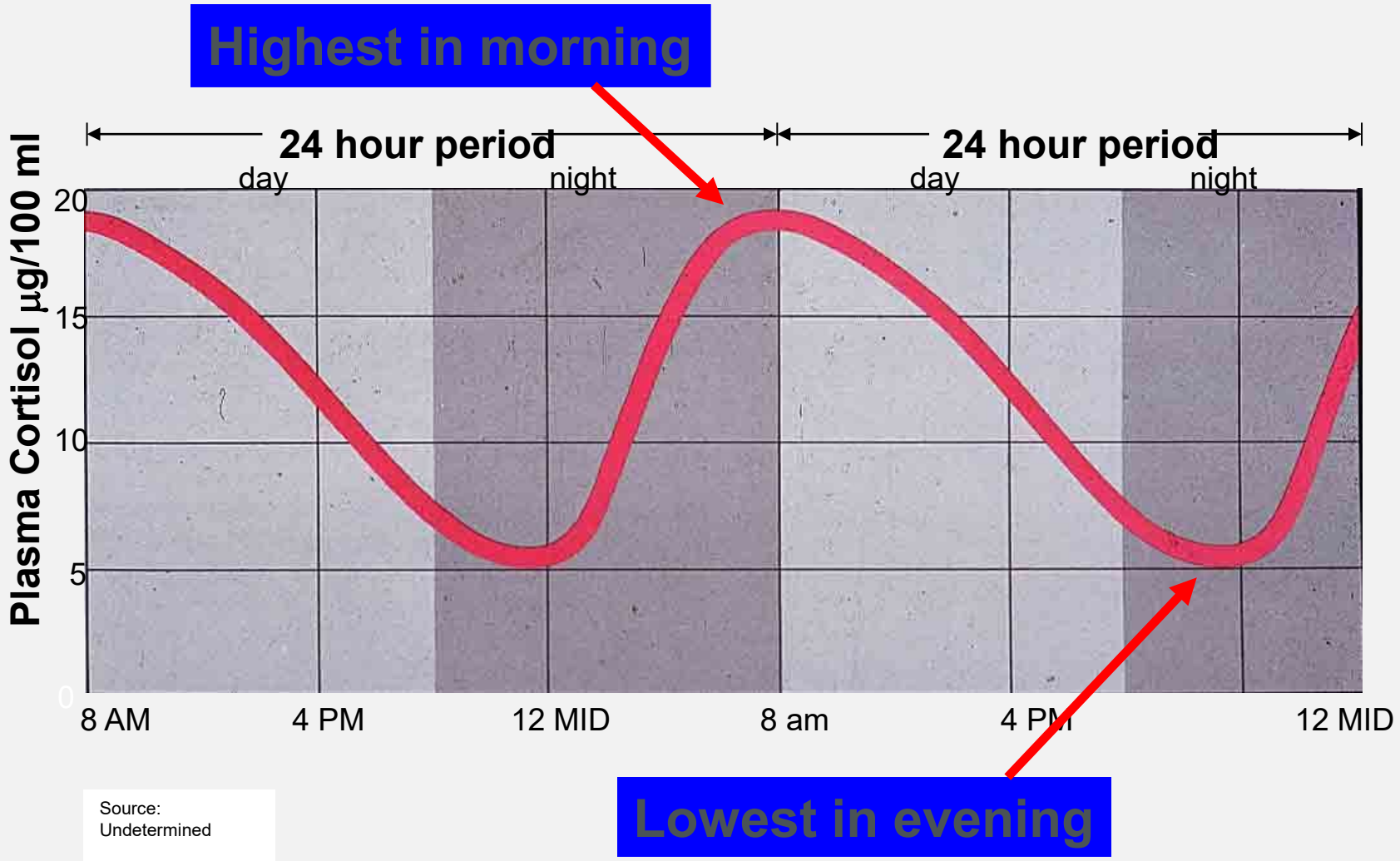
CONFIRM YOUR SUSPICION

INITIAL TEST – AM CORTISOL

- AM Serum Cortisol (7 – 9 am) ***
  - With or without ACTH
- Consider CBG, albumin levels
    - Elevated (OCP use, pregnancy) can falsely increase
    - Low (cirrhosis, nephrotic syndrome, critically ill) can falsely decrease

  - **Rule out if ≥ 18 mcg/dL**
  - Likely AI if < 3-5 ug/dL
    - Stim for confirmation
  - Stim test for indeterminate

Circadian Rhythm of Cortisol Secretion



Source:
Undetermined

CONFIRM- STIM TEST

GIVE 250 MCG
COSYNTROPIN IV/IM/SQ
AND BASELINE CORTISOL

CORTISOL @ 30 MINS

CORTISOL @ 60 MINS

Peak cortisol

- <14 mcg/dL – AI likely
- ≥14 to <18 mcg/dL – depends on test and clinical likelihood
  - DHEAS level may be useful
- ≥18 mcg/dL – AI excluded

PRIMARY
OR
SECONDARY/CENTRAL?

PRIMARY

- Mineralocorticoid deficiency more pronounced
  - Postural hypotension, muscle cramps, salt craving
- Skin pigmentation
- Other AI disorders

SECONDARY

- Weakness, fatigue, muscle/joint pain, and psychiatric symptoms
- Panhypopituitarism
- Headaches/visual symptoms
- History of head trauma/surgery
- Offending meds

Primary >2x ULN

Secondary – low/inappropriately normal

LABORATORY FINDINGS

- Hypoglycemia
- Normocytic anemia, eosinophilia
- TSH elevation, normal T4
  - Lack of GC suppression inhibition of TSH release
- **Secondary AI:**
  - Hypogonadism, hypothyroidism
- **Primary AI:**
  - High renin and low aldosterone
  - Low Na, High K, metabolic acidosis
  - Low DHEAS

DETERMINE CAUSE

PRIMARY ADRENAL INSUFFICIENCY

Most Common

- Autoimmune (~80-90%)
  - ***21-Hydroxylase Ab***
  - 50-65% will have other AI, especially thyroid

Less Common

- Infections
  - TB, fungal, CMV, HIV
- Surgery
- Metastatic
- Hemorrhagic
  - Gram negative sepsis
- Genetic
  - Adrenoleukodystrophy, ACTH resistance
- Medications

Types of endocrine and nonendocrine autoimmune syndromes associated with adrenal insufficiency

Disorder	Prevalence (%)
Polyglandular autoimmune syndrome type 1	
Endocrine	
Hypoparathyroidism	89
Chronic mucocutaneous candidiasis	75
Adrenal insufficiency	60
Primary hypogonadism	45
Hypothyroidism	12
Type 1 diabetes mellitus	1
Hypopituitarism	<1
Diabetes insipidus	<1
Nonendocrine	
Malabsorption syndromes	25
Alopecia totalis or areata	20
Pernicious anemia	16
Chronic active hepatitis	9
Vitiligo	4
Polyglandular autoimmune syndrome type 2	
Endocrine	
Adrenal insufficiency	100
Autoimmune thyroid disease	70
Type 1 diabetes mellitus	50
Primary hypogonadism	5 to 50
Diabetes insipidus	<1

+ 21-HYDROXYLASE

All patients: Evaluate for concurrent autoimmune hypoparathyroidism, diabetes, and hypothyroidism

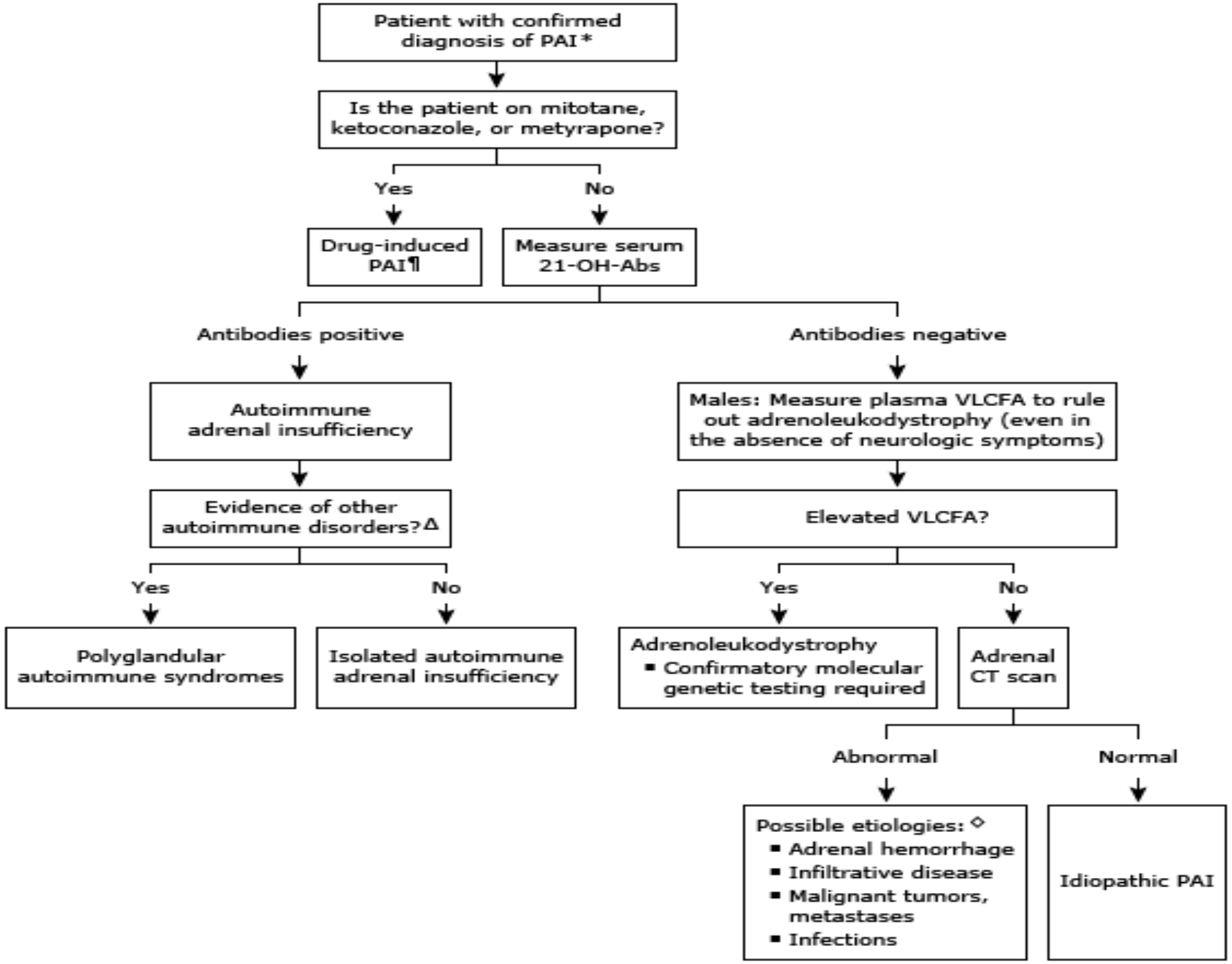
- Calcium, phosphorus, fasting glucose, TSH, free T4 +/- PTH

Females < 48 yo with amenorrhea or oligomenorrhea

- FSH, LH, Estradiol

Males with signs or symptoms of hypogonadism

- LH, testosterone


Patient with confirmed diagnosis of PAI*
Is the patient on mitotane, ketoconazole, or metyrapone?
Yes
No
Drug-induced PAI¶
Measure serum 21-OH-Abs
Antibodies positive
Antibodies negative
Autoimmune adrenal insufficiency
Evidence of other autoimmune disorders?Δ
Yes
No
Polyglandular autoimmune syndromes
Isolated autoimmune adrenal insufficiency
Males: Measure plasma VLCFA to rule out adrenoleukodystrophy (even in the absence of neurologic symptoms)
Elevated VLCFA?
Yes
No
Adrenoleukodystrophy
Confirmatory molecular genetic testing required
Adrenal CT scan
Abnormal
Normal
Possible etiologies:◇
Adrenal hemorrhage
Infiltrative disease
Malignant tumors, metastases
Infections
Idiopathic PAI


NICK NOLTE
SUSAN SARANDON
LORENZO'S OIL

SECONDARY ADRENAL INSUFFICIENCY

Most Common

- **Glucocorticoid induced HPA suppression**
  - > 7.5 mg prednisone equiv for >3 weeks enough to establish as cause

History

- Head trauma/tumors
- Brain surgery/chemo
- Pituitary surgery, autoimmunity,
  - Get MRI
- Meds

TREATMENT

CRITICALLY ILL

- Hyponatremia, hyperkalemia, and hypotension refractory to fluids resuscitation and vasopressors without any clear causation
  - High index of suspicion!
  - Hint: Hypoglycemia, eosinophilia
- **Treat before you diagnose**

ADRENAL CRISIS

- Fluids!
- Hydrocortisone IV/IM 100mg bolus
  - 50mg Q6h x24 hours
- Overreplacement in short term not harmful
- Don’t need fludrocortisone if hydrocortisone > 40 mg
- Underlying cause

Secondary – CG alone

- **Hydrocortisone** 15-25 mg daily in 2-3 doses with 75% in am (BSA: 8-10 mg/m^2)
  - 15 mg am, 5 mg early afternoon
  - 10-5-5
- Monitor clinically, for cushingoid features
- Lowest dose to tx symptoms

Primary AI – All Hormones

- **Hydrocortisone**
- **Fludrocortisone** 50-100 *ug* daily
  - Monitor BP, K+, Renin, symptoms
- +/- Androgen replacement (women)
  - Consider: low libido, depression, low energy
  - DHEAS 50mg daily
    - Reassess in 6 months

GLUCOCORTICOID INDUCED AI

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- 1% of population on chronic GC therapy
  - Up to 50% of these patients at risk for AI when stopped abruptly
- Differentiate between GC withdrawal syndrome and recurrence of disease
  - *Only occurs once on physiologic doses*

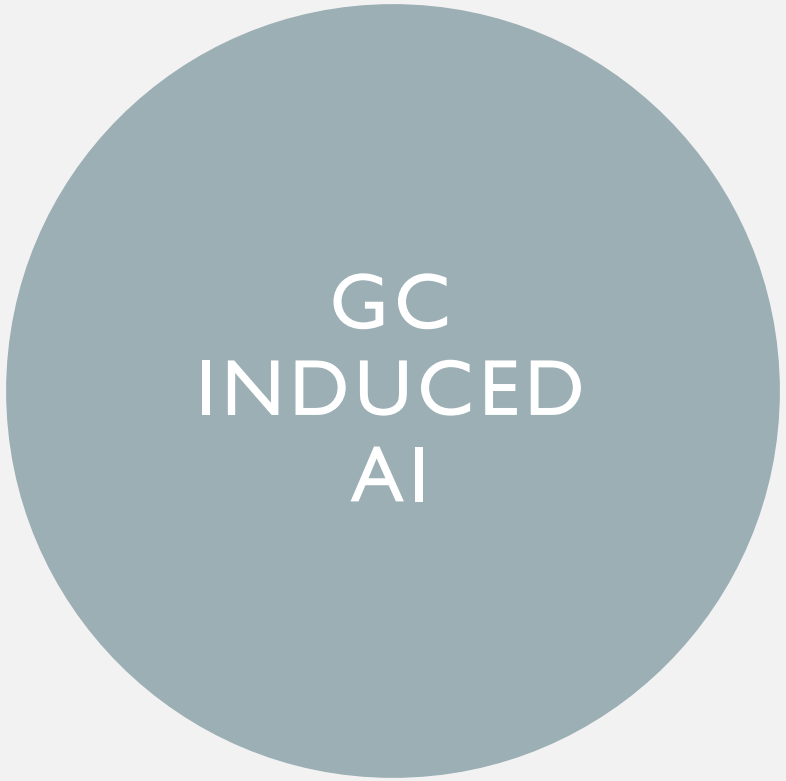


Table 5. Clinical features of adrenal insufficiency, glucocorticoid withdrawal syndrome and common underlying conditions

	Glucocorticoid withdrawal syndrome	Adrenal insufficiency	Underlying condition for which glucocorticoids were initially prescribed
Symptoms	General malaise, fatigue, nausea, muscle and joint pain, sleep disturbances, mood change	General malaise, fatigue, nausea, muscle and joint pain	Depending on condition (eg, joint pain in rheumatoid arthritis). Common overlapping symptoms (general malaise, fatigue)
Signs	Cushingoid features common, especially earlier in the glucocorticoid taper	Weight loss[a], hypotension, orthostasis	Disease-specific signs reappear
Timing of symptoms and signs occurrence	At any point during glucocorticoid taper, usually when prednisone is decreased <15 mg/day Higher risk with long-term supraphysiologic glucocorticoid therapy	Only when not treated with optimal glucocorticoid therapy (subphysiologic glucocorticoid dose, increased glucocorticoid requirements due to sickness)	At any point during glucocorticoid taper if the underlying condition is sub-optimally controlled with a non-glucocorticoid agent
Biochemistry	Normal electrolytes Glucocorticoid-induced hyperglycemia may be present	Hyponatremia, hypoglycemia	Biomarkers of disease activity (sedimentation rate, disease-specific biomarkers)
HPA axis	Testing is not recommended If tested, ACTH and cortisol are usually undetectable	Initially, low ACTH and cortisol Later in recovery: normal-elevated ACTH, low cortisol	Not applicable
Risk of adrenal crisis	Unlikely, if glucocorticoids are administered (as patients with glucocorticoid withdrawal syndrome also have adrenal insufficiency)	Yes, if not optimally treated with glucocorticoid therapy	Not applicable

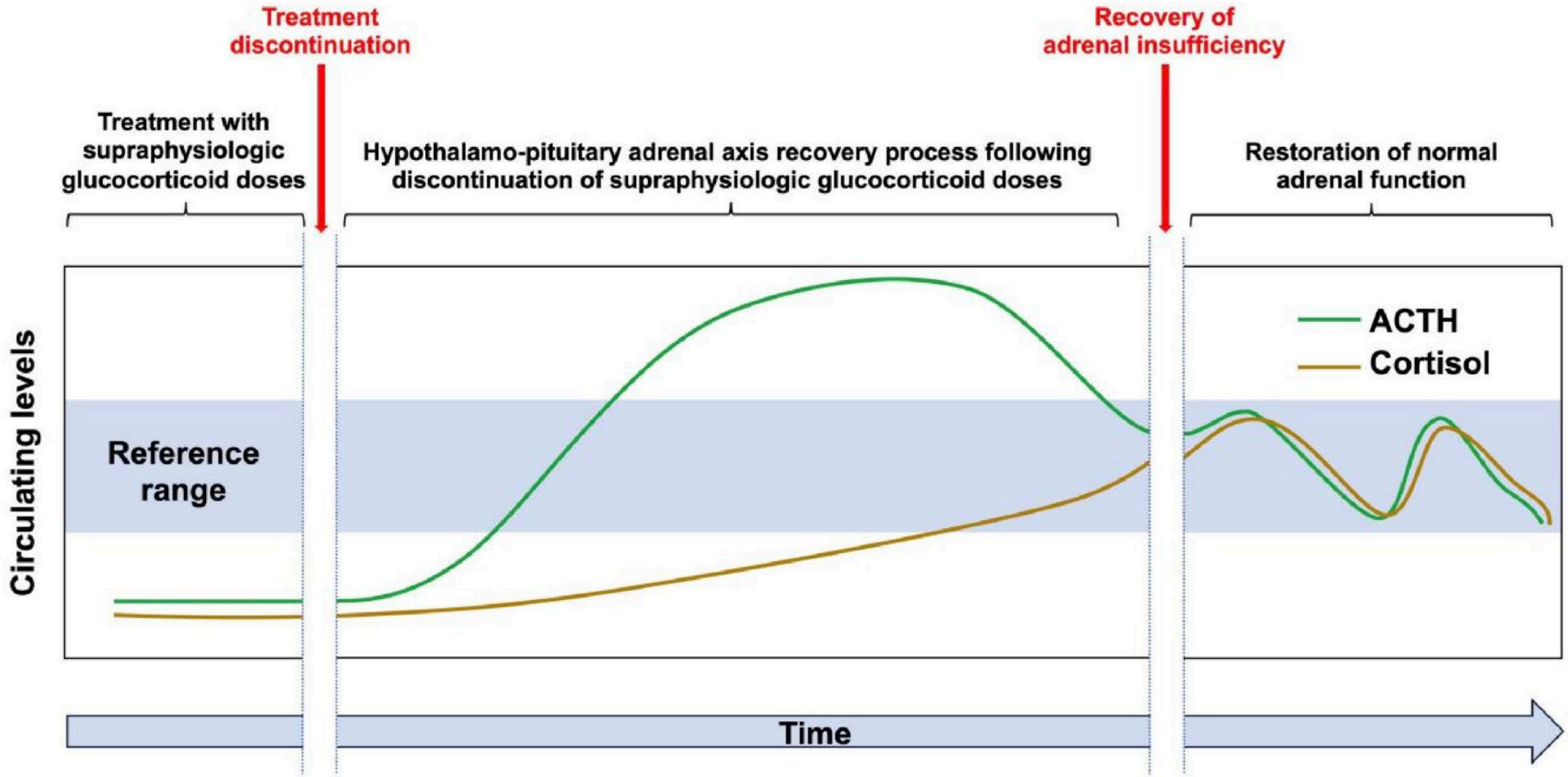
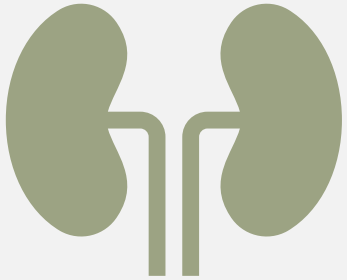


Figure 1. Schematic representation of HPA axis recovery following discontinuation of supraphysiologic glucocorticoid therapy (adapted from: Prete and Bancos 2021 (58)).

Table 3. Risk factors for developing adrenal insufficiency, and susceptibility to adrenal crisis, during glucocorticoid therapy and withdrawal from therapy

Factors	Risk for adrenal insufficiency and crisis		
	Low	**Moderate**	**High**
Glucocorticoid potency	Hydrocortisone Cortisone acetate Deflazacort	Prednisone Prednisolone Methylprednisolone Triamcinolone	Dexamethasone Betamethasone Fluticasone
Administration Route	Nasal Topical Ophthalmic	Inhaled	Systemic (oral, intramuscular, I intravenous) Intra-articular Concurrent use of differently aadministered glucocorticoid
Dose	Low	Medium	High
Duration of use	<3-4 weeks	3-4 weeks-3 months	>3 months
Body Mass Index (64)	Normal	Overweight	Obese
Age (65)	Younger adults		Older adults

SUPRAPHYSIOLOGIC DOSES



> Hydrocortisone equivalent of 15-25 mg

4-6 mg Prednisone

3-5 mg Methylpred

0.25-0.5 mg Dexamethasone

Table 1. Pharmacologic characteristics of commonly prescribed systemic glucocorticoids (19-23)

Glucocorticoids	Approximate equivalent dose[a]	Glucocorticoid potency (relative to hydrocortisone)[a, b]	Plasma half-life (min)[a, c]	Biological half-life (hours)[a]
Short-acting glucocorticoids with lower potency				
Hydrocortisone	20 mg	1.0	90-120	8-12
Cortisone acetate	25 mg	0.8	80-120	8-12
Deflazacort	7.5 mg	1.0	70-120	Not defined
Intermediate-acting glucocorticoids with moderate potency				
Prednisone	5 mg	4.0	60	12-36
Prednisolone	5 mg	4.0	115-200	12-36
Triamcinolone	4 mg	5.0	30	12-36
Methylprednisolone	4 mg	5.0	180	12-36
Long-acting glucocorticoids with highest potency				
Dexamethasone	0.5 mg	30-60	200	36-72
Betamethasone	0.5 mg	25-40	300	36-72

RISK - DOES ROUTE MATTER?

- 4.2% (95% CI 0.5-28.9) for nasal
- 48.7% (95% CI 36.9-60.6) for oral use
- 52.2% (95% CI 40.5-63.6) for intra-articular

***Biochemically defined, unclear clinical relevance*

Table 6. Non-oral glucocorticoid formulations and risk of glucocorticoid-induced adrenal insufficiency

	Prevalence of glucocorticoid-induced adrenal insufficiency[a]	Factors increasing the risk of glucocorticoid-induced adrenal insufficiency	Strategies to mitigate the risk of glucocorticoid-induced adrenal insufficiency[b]
Inhaled glucocorticoids	• Overall: 7.8% (CI 4.2-13.9) • Short-term use (<1 month): 1.4% (CI 0.3-7.4) • Medium-term use (1-12 months): 11.9% (CI 5.8-23.1) • Long-term use (>12 months): 27.4% (CI 17.7-39.8) • Low dose use: 2.4% (0.6-9.3) • Intermediate dose use: 8.5% (4.2-16.8) • High dose[c] use: 21.5% (12.0-35.5)	• Treatment with high doses[c] for prolonged periods • Use of fluticasone propionate • Concomitant use of other glucocorticoid formulations (eg, oral glucocorticoids in chronic obstructive pulmonary disease or nasal glucocorticoids for rhinitis/nasal polyposis) • Lower body mass index • Higher compliance with treatment • Concomitant treatment with strong cytochrome P450 3A4 inhibitors[d] (eg, medications containing ritonavir; antifungal drugs for acute allergic bronchopulmonary aspergillosis)	• Use the lowest effective glucocorticoid dose for the shortest period • Use spacers and mouth rinsing • Consider alternative glucocorticoids to fluticasone propionate • Avoid co-administration with strong cytochrome P450 3A4 inhibitors[d]
Intra-articular glucocorticoids	52.2% (40.5-63.6)	• Repeated injections over a short period (<3 months) • Simultaneous injections of multiple joints • Use of high glucocorticoid doses • Inflammatory arthropathies • Concomitant use of other glucocorticoid formulations • Concomitant treatment with strong cytochrome P450 3A4 inhibitors[d]	• Reduce the number of injections, if possible • Space out injections by at least 3-4 months, if possible • Triamcinolone hexacetonide may carry a lower risk of systemic absorption than triamcinolone acetonide • Avoid co-administration with strong cytochrome P450 3A4 inhibitors[d]
Percutaneous (topical) glucocorticoids	4.7% (CI 1.1-18.5)	• Long-term use of high-potency glucocorticoids on large surface areas or areas of increased absorption (eg, mucosa) • Prolonged use on inflamed skin with impaired barrier function • Occlusive dressings • Use on mucous membranes, eyelids, and scrotum • Concomitant use of other glucocorticoid formulations • Concomitant treatment with strong cytochrome P450 3A4 inhibitors[d]	• Use the smallest effective quantity for the shortest period • Use lower potency glucocorticoids, if possible • Avoid co-administration with strong cytochrome P450 3A4 inhibitors[d]
Intra-nasal glucocorticoids	4.2% (CI 0.5-28.9)	• Long-term use • Concomitant use of other glucocorticoid formulations • Concomitant treatment with strong cytochrome P450 3A4 inhibitors[d]	• Use the lowest effective glucocorticoid dose for the shortest period • Avoid co-administration with strong cytochrome P450 3A4 inhibitors[d]

- Fluticasone propionate >500 µg/day
- Beclometasone dipropionate (standard particle inhalers) > 1000 µg/day
- Beclometasone dipropionate (extra fine particle inhalers) > 400 µg/day
- Budesonide >800 µg/day
- Ciclesonide >320 µg/day
- Fluticasone furoate >200 µg/day
- Mometasone furoate standard particle >400 µg/day

MANAGING GC INDUCED ADRENAL INSUFFICIENCY

- Only taper once underlying disease controlled
- Don’t test for AI in patients on supraphysiologic doses of steroids
- Don’t taper if <3-4 weeks, irrespective of dose
  - ?GC withdrawal?

TREAT

- Fast taper for doses in supraphysiologic range, slower once physiologic range
- Switch long acting GC (dexamethasone, betamethasone) to shorter acting GC (hydrocortisone, prednisone)

APPROACH

- Gradual taper and monitor for symptoms
- Test morning cortisol to assess HPA axis

ASSESSING HPA AXIS

Test morning cortisol 8-9 am (after 24 hour steroid washout)

- Continuum (higher values indicative of HPA recovery)
  - Recovery if am cortisol >10 ug/dL
  - If 5-10, continue dose and repeat in weeks-months
  - <5 dose continued and repeat in a few months

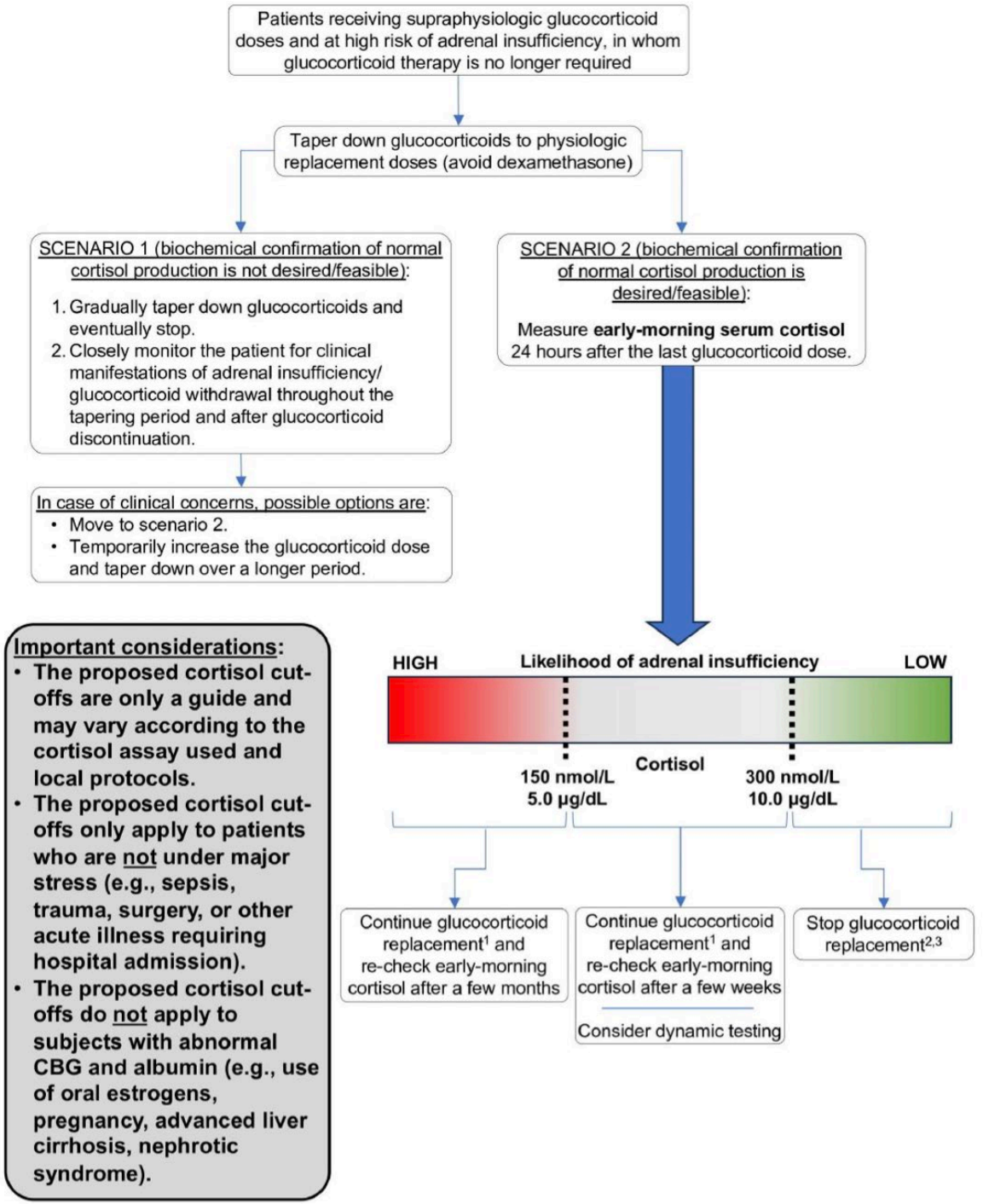

Patients receiving supraphysiologic glucocorticoid doses and at high risk of adrenal insufficiency, in whom glucocorticoid therapy is no longer required
Taper down glucocorticoids to physiologic replacement doses (avoid dexamethasone)
SCENARIO 1 (biochemical confirmation of normal cortisol production is not desired/feasible):
1. Gradually taper down glucocorticoids and eventually stop.
2. Closely monitor the patient for clinical manifestations of adrenal insufficiency/ glucocorticoid withdrawal throughout the tapering period and after glucocorticoid discontinuation.
In case of clinical concerns, possible options are:
• Move to scenario 2.
• Temporarily increase the glucocorticoid dose and taper down over a longer period.
SCENARIO 2 (biochemical confirmation of normal cortisol production is desired/feasible):
Measure early-morning serum cortisol 24 hours after the last glucocorticoid dose.
Important considerations:
• The proposed cortisol cut-offs are only a guide and may vary according to the cortisol assay used and local protocols.
• The proposed cortisol cut-offs only apply to patients who are not under major stress (e.g., sepsis, trauma, surgery, or other acute illness requiring hospital admission).
• The proposed cortisol cut-offs do not apply to subjects with abnormal CBG and albumin (e.g., use of oral estrogens, pregnancy, advanced liver cirrhosis, nephrotic syndrome).
HIGH
Likelihood of adrenal insufficiency
LOW
Cortisol
150 nmol/L
5.0 µg/dL
300 nmol/L
10.0 µg/dL
Continue glucocorticoid replacement[1] and re-check early-morning cortisol after a few months
Continue glucocorticoid replacement[1] and re-check early-morning cortisol after a few weeks
Consider dynamic testing
Stop glucocorticoid replacement[2,3]

Table 4. Suggested tapering regimen depending on glucocorticoid dose

Patient's current daily prednisone equivalent dose	Suggested prednisone decrements	Time interval
>40 mg	5-10 mg decrease	Every week
20-40 mg	5 mg decrease	Every week
10-20 mg	2.5 mg decrease	Every 1-4 weeks
5-10 mg	1 mg decrease	Every 1-4 weeks
5 mg	In absence of clinical symptoms or negative testing for adrenal insufficiency continue 1 mg decrease (if low dosage prednisolone preparations are not available, alternative: 20 mg hydrocortisone with 5 mg decrease)	Every 4 weeks

ILLNESS DOSING – ALL PT WITH AI

Double dose

- Mild illness (sore throat, runny nose)
- Major Dental Work (extractions / root canals)
- Invasive Diagnostic Procedures

Triple the dose

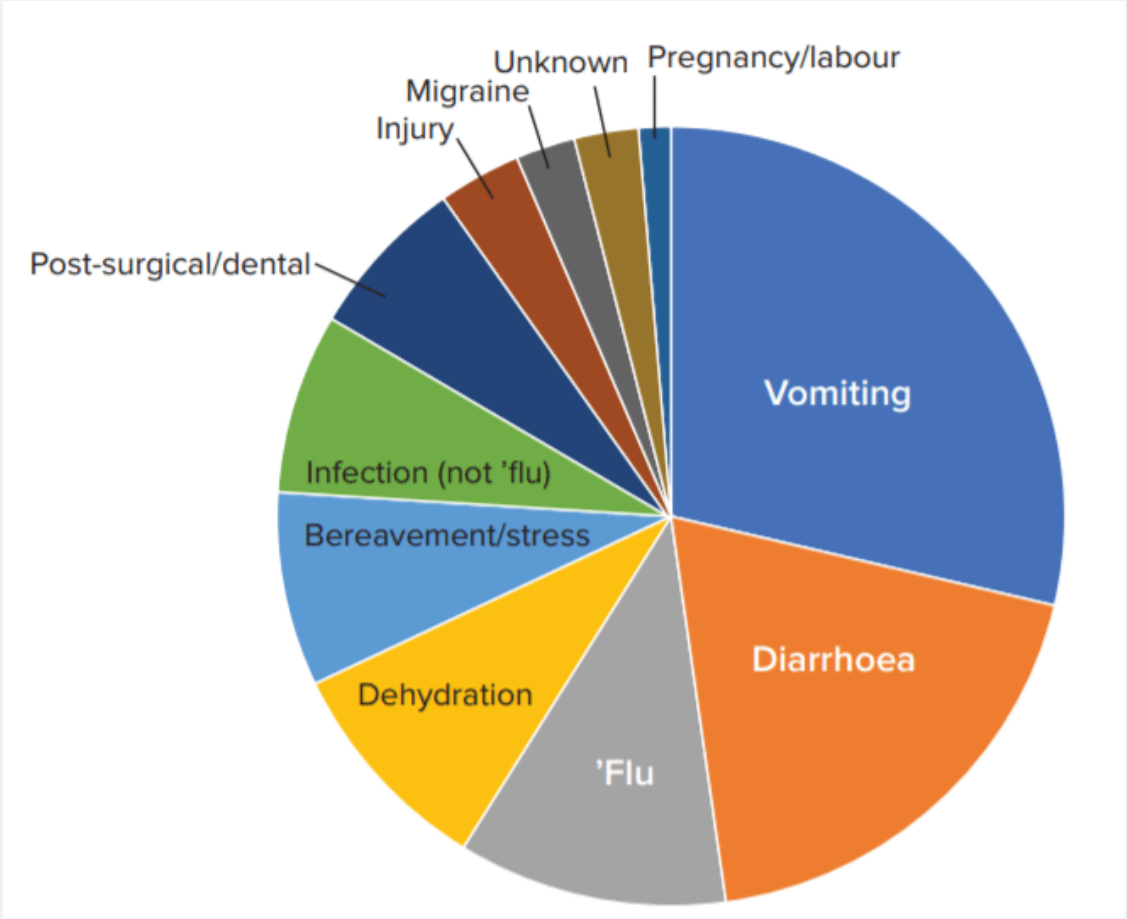
- Febrile illness

Vomiting / Diarrhea

- Poor Absorption
- "Emergency Pack" or ER visit
  - Prefilled 100mg hydrocortisone syringe; Subcut admin
  - Go to the hospital

Exercise

- Additional 5-10mg prior to any major physical exercise

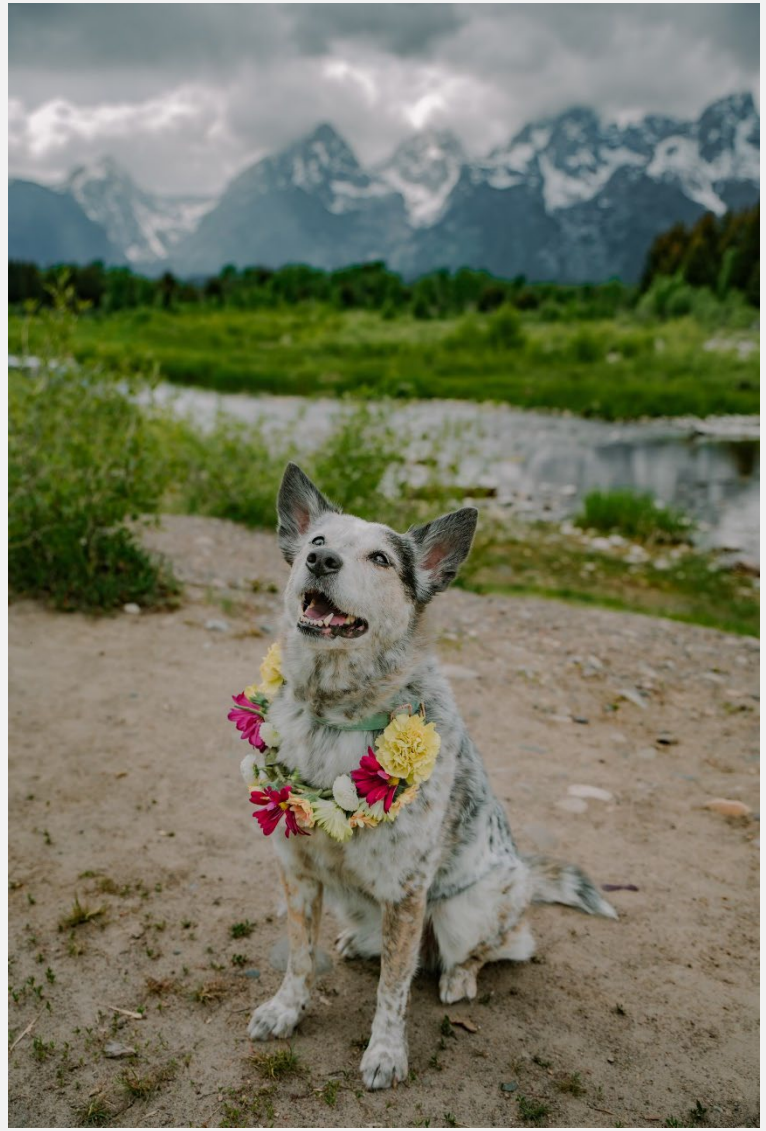


https://www.nadf.us/uploads/1/3/0/1/130191972/nadf_stress-dosing_guidelines.pdf

SUMMARY

- Symptoms of AI are **non-specific**
- Most common cause **glucocorticoid HPA suppression** overall
- **Autoimmune** cause most likely in primary AI – evaluate for other autoimmune do
- Suspect in **severely ill** patient w/ CV instability -> high mortality
  - **Treat empirically** while waiting for results of testing
- Start with am serum **cortisol +/- ACTH** then stim
- Use lowest possible dose to control sx's
- Education pt on **Illness / Stress Dosing** recommendations

Questions?



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