Diagnosis and Treatment of adrenal insufficiency in adults

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Outlines:

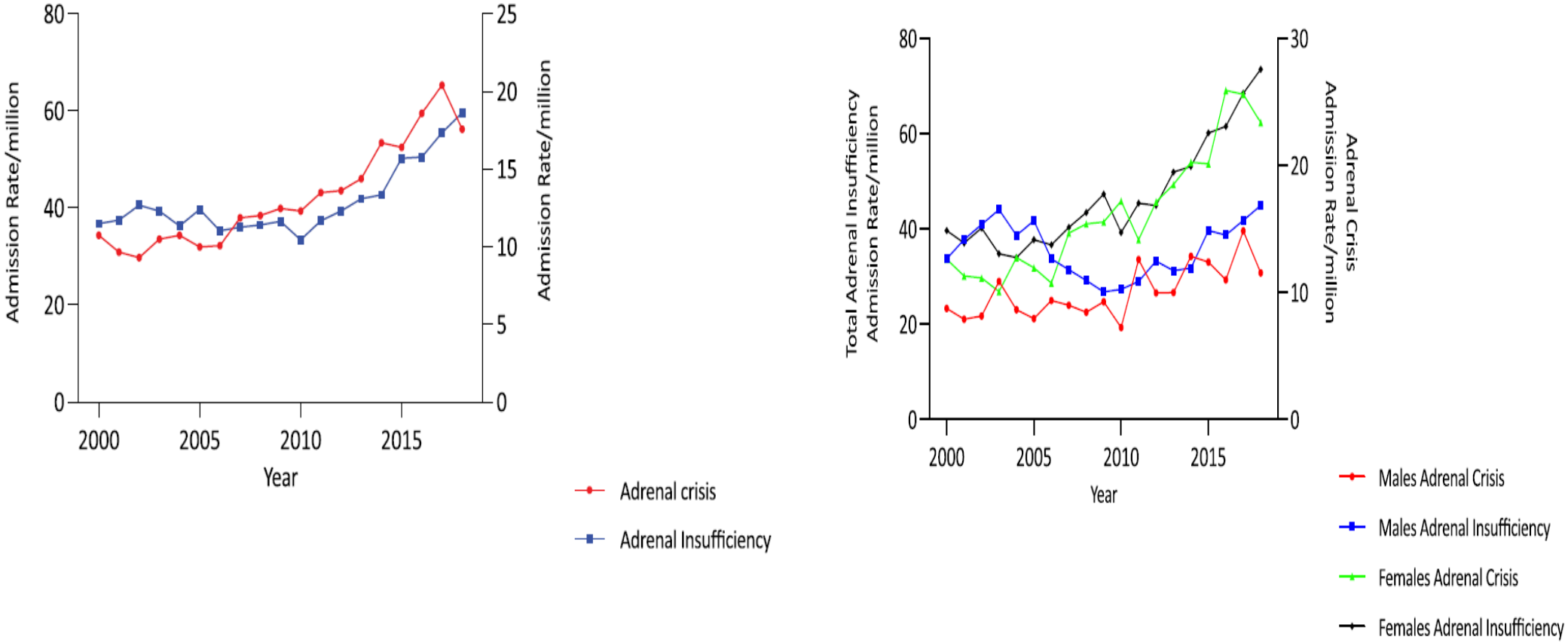
- General principles
- Diagnosis
- Treatment

Addison Disease

Thomas Addison described the condition now known as *primary hypoadrenalism* in his classic monograph published in 1855.

Addison disease is a rare condition with an estimated incidence in the developed world of 0.8 cases per 100,000 and a prevalence of 4 to 11 cases per 100,000 population. Nevertheless, it is associated with significant morbidity and a twofold excess mortality rate , but once the diagnosis is made it can be easily treated. Despite treatment, however, patients carry significant burden of metabolic and psychologic comorbidities.

Adjusted total adrenal insufficiency (AI) and adrenal crisis (AC) admission rates/million population year in Australia



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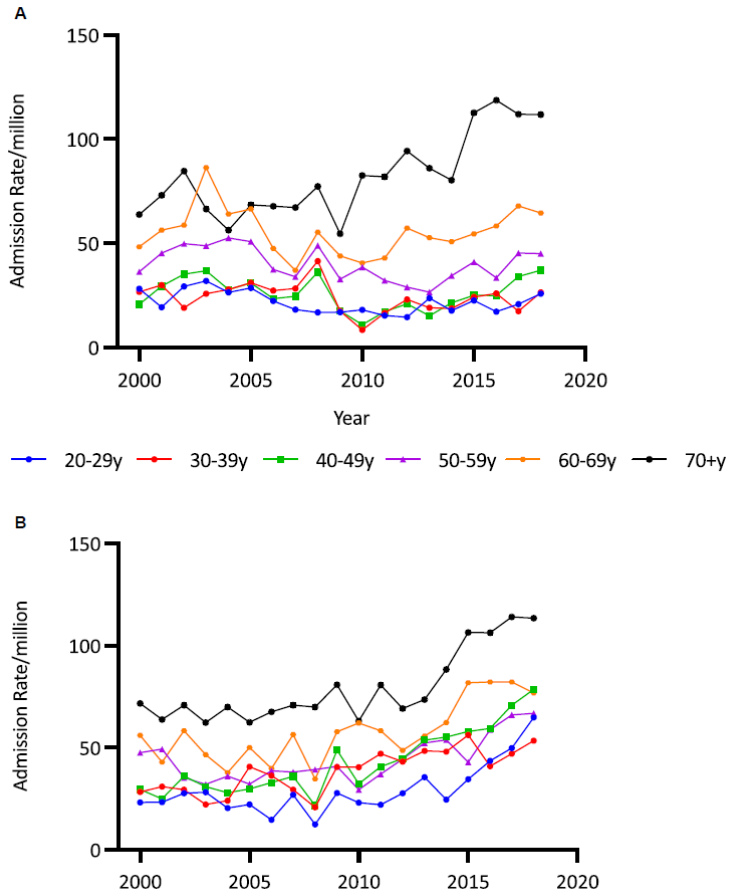
Contributory factors include an increase in iatrogenic AI:

- Use of immunotherapies for malignant disease, more common in older people
- Greater use of cranial imaging leading to increased detection of pituitary adenomas (treatment-related)
- Augmented use of opioids and inhaled corticosteroids
- Increased use over time of the recommended lower doses of short-acting GCs .



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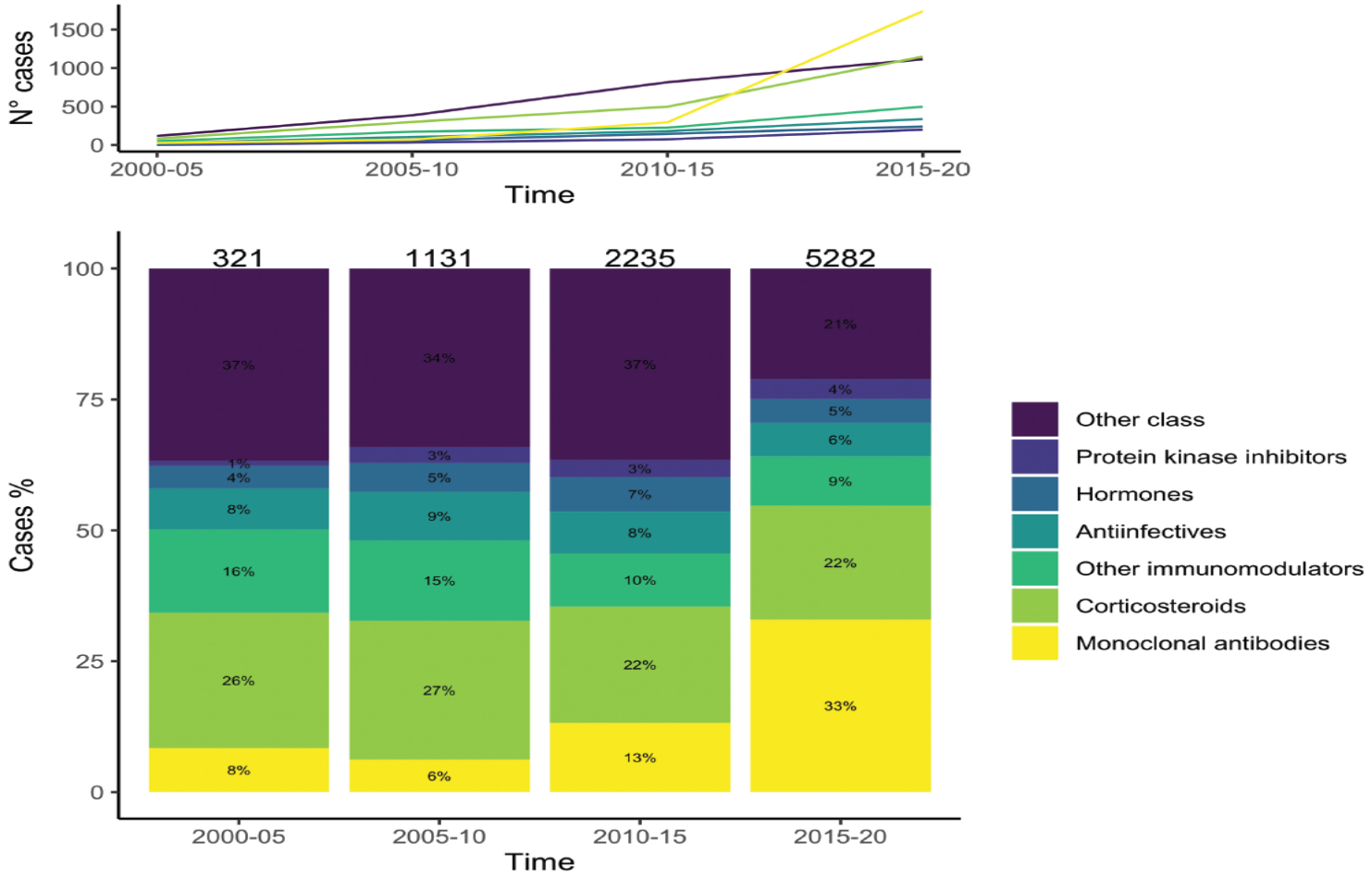
The Changing Face of Drug-induced Adrenal Insufficiency in the FDA Adverse Event Reporting System



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Immune Checkpoint Inhibitor-Induced Adrenalitis and Primary Adrenal Insufficiency

- Immune checkpoint inhibitors (ICIs) targeting cytotoxic T-lymphocyte antigen 4 or programmed death 1 and its ligand (programmed death ligand 1) have been approved for the treatment of a variety of cancers.
- However, ICI therapy is associated with a risk of immune-related adverse events. This study, reviewed reported cases of adrenalitis and primary adrenal insufficiency .
- PAI often coexists with other endocrinopathies and requires mineralocorticoid as well as glucocorticoid replacement. Even after withdrawal of ICIs, PAI can persist and requires lifelong replacement therapy.

Endocrine Practice
Volume 27, Issue 2, February 2021, Pages 165-169

Clinical presentation of acute adrenal insufficiency

➢Symptoms

- Abdominal pain
- Nausea
- Myalgia
- Weight loss
- Fatigue
- Dizziness

➢On examination

- Hypotension/shock
- Fever
- Skin hyperpigmentation (primary adrenal insufficiency only)

➢Biochemistry

- Hyponatraemia
- Hyperkalaemia
- ↑Urea
- Metabolic acidosis
- ↑TSH
- Hypercalcaemia (uncommon)
- Hypoglycaemia (more common in children)
- Lymphocytosis
- Eosinophilia

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Causes of adrenal insufficiency

➢Primary adrenal insufficiency

- **Autoimmune:** Isolated adrenal insufficiency (Addison's), APS1 ,APS2
- **Infections:** Tuberculosis, fungal infiltration, AIDS
- **Genetic:** Adrenoleukodystrophy, congenital adrenal hyperplasia, adrenal hypoplasia congenita
- **Vascular:** Adrenal infarction / haemorrhage (Waterhouse- Friedrichson syndrome in meningococcal sepsis)
- **Infiltrative:** Metastasis, lymphoma, sarcoidosis, amyloidosis, haemachromatosis
- **Iatrogenic:** Surgical adrenalectomy or drug induced (eg mitotate, etomidate, ketoconazole, immunotherapy)

➢Secondary adrenal insufficiency

- **Tumour:** Pituitary macroadenoma, other tumour (craniopharyngioma, meningioma)
- **Iatrogenic:** Pituitary irradiation, drugs (opioids, glucocorticoids, immunotherapy)
- **Vascular:** Apoplexy, Sheehan's syndrome
- **Infiltrative:** Tuberculosis, sarcoidosis, histiocytosis X, granulomatosis with polyangiitis, lymphocytic hypophysitis
- **Trauma**
- **GenetiC**

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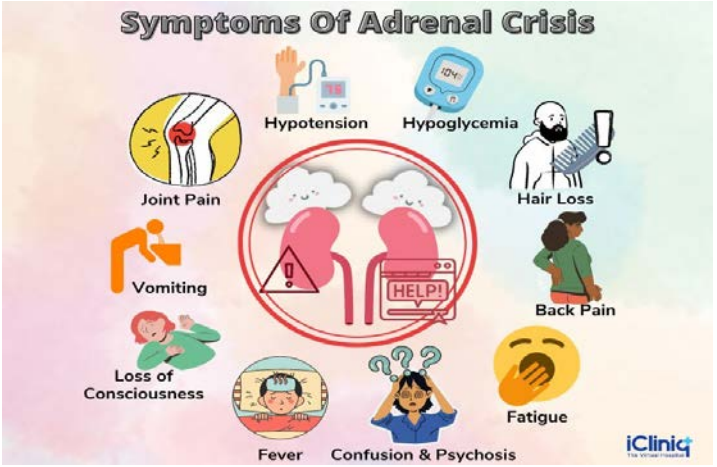
Clinical and laboratory findings suggesting adrenal crisis



Dehydration, hypotension, or shock out of proportion to severity of current illness
Nausea and vomiting with a history of weight loss and anorexia
Abdominal pain, so-called "acute abdomen"
Unexplained hypoglycemia
Unexplained fever
Hyponatremia, hyperkalemia, azotemia, hypercalcemia, or eosinophilia
Hyperpigmentation or vitiligo
Other autoimmune endocrine deficiencies, such as hypothyroidism or gonadal failure

Clin Endocrinol Metab 1985; 14:947.

Diagnosis of adrenal insufficiency

- In adrenal crisis, diagnostic tests should never delay hydrocortisone treatment
- In many cases a low baseline cortisol (often <3.6 µg/dl) alongside raised ACTH can be enough to diagnose primary adrenal insufficiency.
- Cosyntropin stimulation testing can be used to confirm the diagnosis. It is a measure of adrenal reserve and the HPA axis.
- Concerns have been raised about false positive diagnoses of adrenal insufficiency if relying on 30-minute cortisol values in isolation and clinical judgement is required when interpreting the results, taking into account pre-test probability.
- It is important to note that this test is not reliable in diagnosing secondary adrenal insufficiency within 2 weeks of pituitary surgery.
- In sepsis or severe illness, the interpretation of cortisol levels should take into account the underlying stress.

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High CBG

- In women taking oral contraceptives, the serum total cortisol is approximately 1.5 times higher than women not taking oral contraceptives.
- In the setting of possible high corticosteroid-binding globulin (CBG; eg, oral contraceptive use, pregnancy), it is useful to measure CBG or discontinue OCP for6-8 weeks.
- Only a frankly subnormal cortisol value (≤3 mcg/dL [83 nmol/L]) is useful to make the diagnosis of adrenal insufficiency. Values >3 mcg/dL neither confirm nor exclude a diagnosis of adrenal insufficiency.

Clin Endocrinol (Oxf). 2007;66(5):632.

Low CBG

- Serum cortisol in patients with suspected low corticosteroid-binding globulin (CBG) due to nephrotic syndrome, sepsis, or cirrhosis should be interpreted with caution.
- Patients with cirrhosis or nephrotic syndrome who have low CBG values may have "subnormal" morning cortisol and cortisol response to ACTH in the absence of adrenal insufficiency .
- In this setting, use salivary cortisol levels to assess for adrenal insufficiency. Assay-specific cutoff points for basal or ACTH-stimulated values must be used .

J Clin Endocrinol Metab. 2007;92(4):1326. Epub 2007 Jan 23.

Approach to interpreting the peak serum cortisol value after ACTH administration

- <14 mcg/dL– Adrenal insufficiency likely.
- ≥14 to <18 mcg/dL– The interpretation of the cortisol result depends on the type of assay that is used to measure it and the clinical likelihood of adrenal insufficiency in an individual patient.
  - If the assay type is unknown or diagnosis is uncertain, a DHEAS level may be useful. A normal DHEAS (using an age- and sex-specific reference range) makes adrenal insufficiency unlikely.
- ≥18 mcg/dL– Adrenal insufficiency generally excluded regardless of assay used to measure cortisol.

J Endocr Soc. 2021;5(4):bvab022. Epub 2021 Feb 18

Partial ACTH deficiency

- Corticotropin (ACTH) deficiency occurring after pituitary surgery, hypothalamic-pituitary radiotherapy, trauma, or opioid use may be partial. Partial ACTH deficiency has also been reported after discontinuation of glucocorticoids, including inhaled preparations .
- Partial ACTH deficiency usually causes symptoms during times of physical stress (eg, febrile illness) when corticotropin-releasing hormone (CRH) and/or ACTH secretion do not increase in response to the stress. However, basal ACTH production may be adequate to prevent adrenal gland atrophy and, therefore, ACTH-stimulated cortisol levels may be normal.

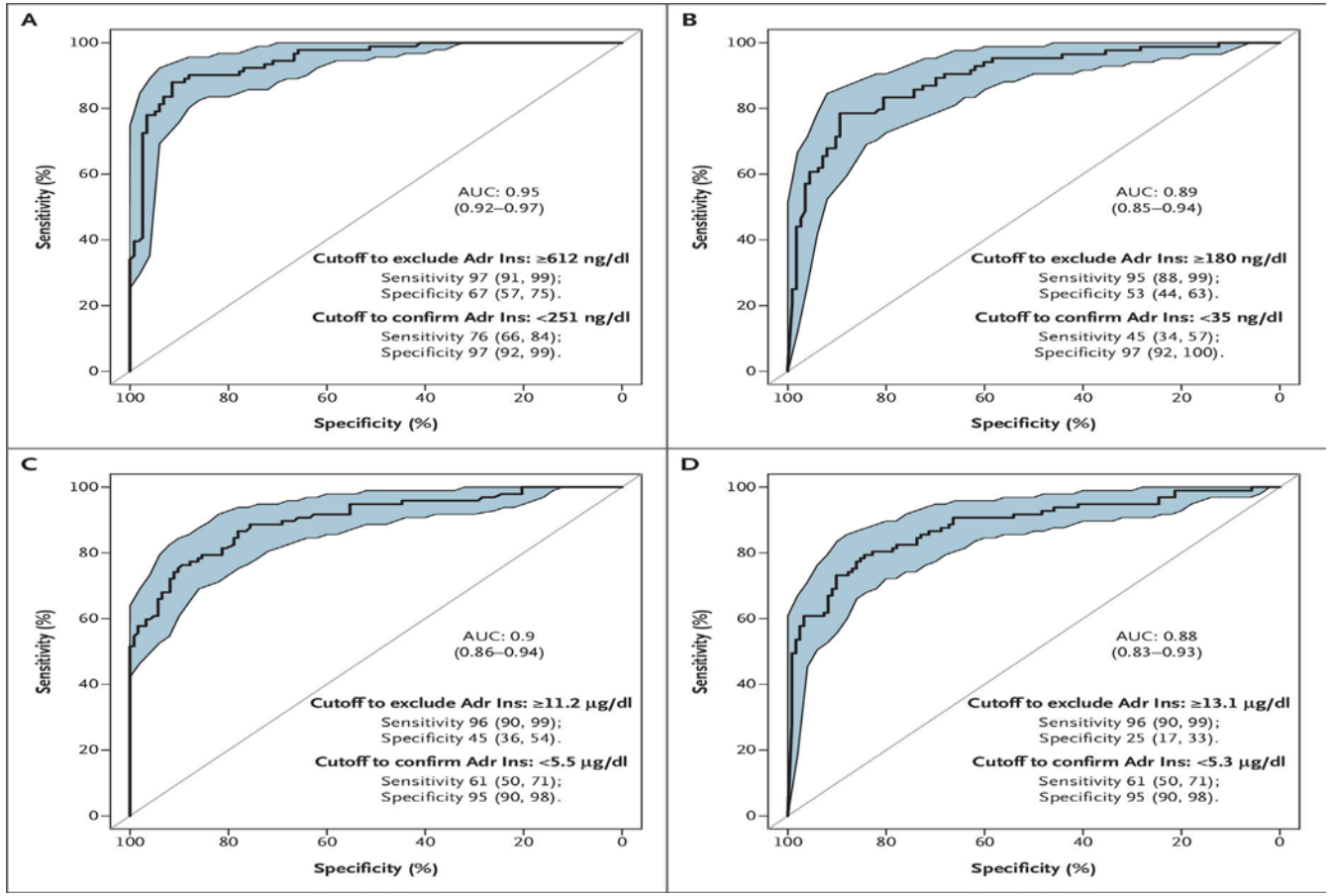
BMJ. 2021;374:n1380. Epub 2021 Jul 12.

Opioid-induced adrenal insufficiency

- Long-term opioid use for the treatment of chronic pain may cause chronic central adrenal insufficiency due to opioid suppression of the HPA axis .
- Opioid-induced adrenal insufficiency should be suspected in people chronically taking opioids who have fatigue, postural hypotension, nausea, weight loss, and hypogonadism .
- If it is recent, (insulin-induced hypoglycemia test) or a trial of glucocorticoid replacement is warranted.

Mayo Clin Proc. 2018;93(7):937.

Home Waking Salivary Cortisone to Screen for Adrenal Insufficiency



NEJM Evid 2023;2(2)

- Waking salivary cortisone (Panel A), waking salivary cortisol (Panel B), baseline serum cortisol by immunoassay (Panel C), and baseline serum cortisol by liquid chromatography–tandem mass spectrometry (Panel

Diagnosis of adrenal insufficiency

- Insulin tolerance test is the gold standard for identifying secondary adrenal insufficiency, if suspected.
- ITT is contraindicated in those with heart disease, seizures , severe hypothyroidism and in those with baseline cortisol <3.6µg/dl.
- Alternatives include glucagon stimulation test or metyrapone suppression test.
- Oral estrogen should be discontinued 6 weeks beforehand.
- No oral steroid medications should be administered 24 hours prior to the test.
- Steroid creams and inhalers should ideally also be avoided if possible.

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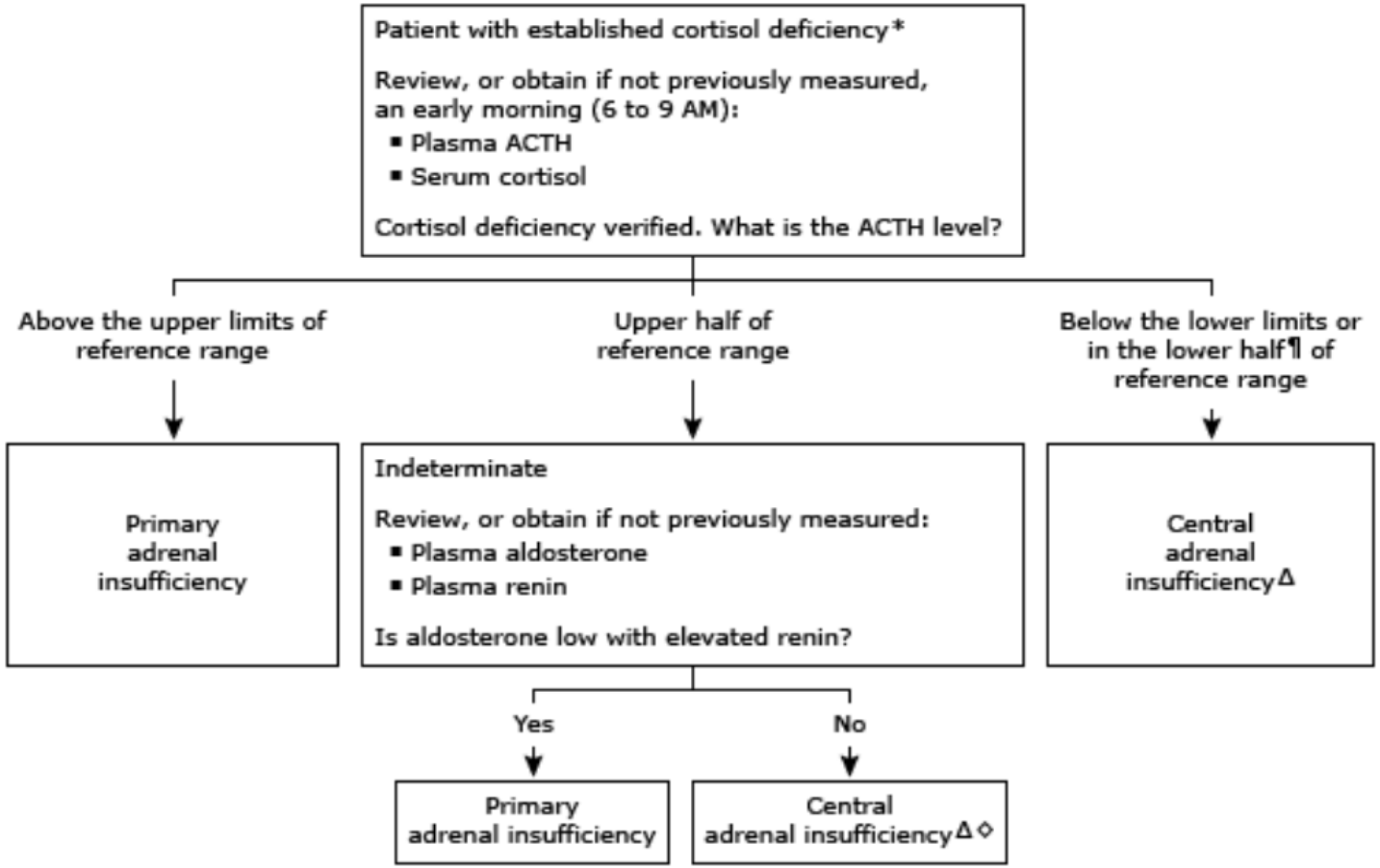
Insulin induced hypoglycemia test (ITT)

- **Procedure** — The patient fasts for at least eight hours before the test and must remain supine during the procedure. An experienced clinician must be present at all times to monitor for complications related to hypoglycemia (chest pain, tachycardia, and/or neuroglycopenic symptoms [confusion, seizures]). A syringe containing 50 percent glucose solution should be at the bedside. An intravenous line is established, and insulin is injected intravenously. The usual dose is 0.15 units/kg of regular insulin, but different doses may be indicated in certain patients:
- In patients thought to have hypopituitarism or primary adrenal insufficiency, the insulin dose is decreased to 0.1 units/kg because these conditions may be associated with decreased release of other counterregulatory hormones such as epinephrine and growth hormone.
- In patients with obesity, diabetes mellitus, suspected acromegaly or Cushing's syndrome, the dose is increased to 0.2 units/kg. However, coronary disease must be ruled out before performing the test, particularly at this higher dose.
- In premenopausal women, the test can be performed at any phase of the menstrual cycle

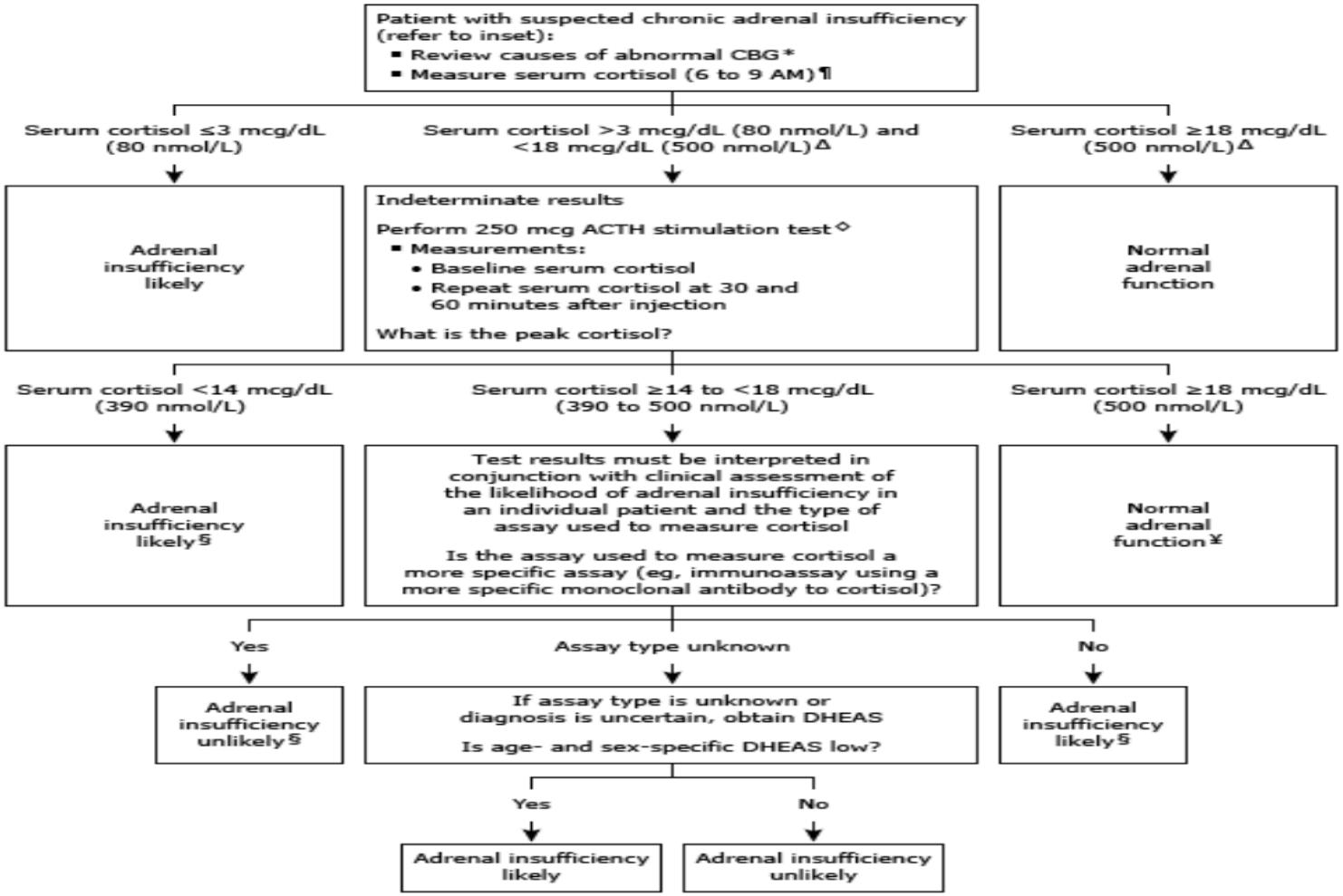
Insulin induced hypoglycemia test (ITT)

- Blood is obtained for bedside measurement of serum glucose and for laboratory measurement of serum glucose and cortisol levels (and for plasma corticotropin [ACTH], if indicated) immediately before insulin is injected and every 15 minutes thereafter. The final, definitive blood sample for measurement of ACTH and cortisol should be obtained 5 to 10 minutes after the patient begins to perspire or, if it can reliably be measured, when the serum glucose falls below 35 mg/dL . As noted, there is no clear consensus about the glucose nadir necessary for optimal test performance. While many use 35 mg/dL , others use 40 or 45 mg/dL .

Distinguishing between primary and central adrenal insufficiency

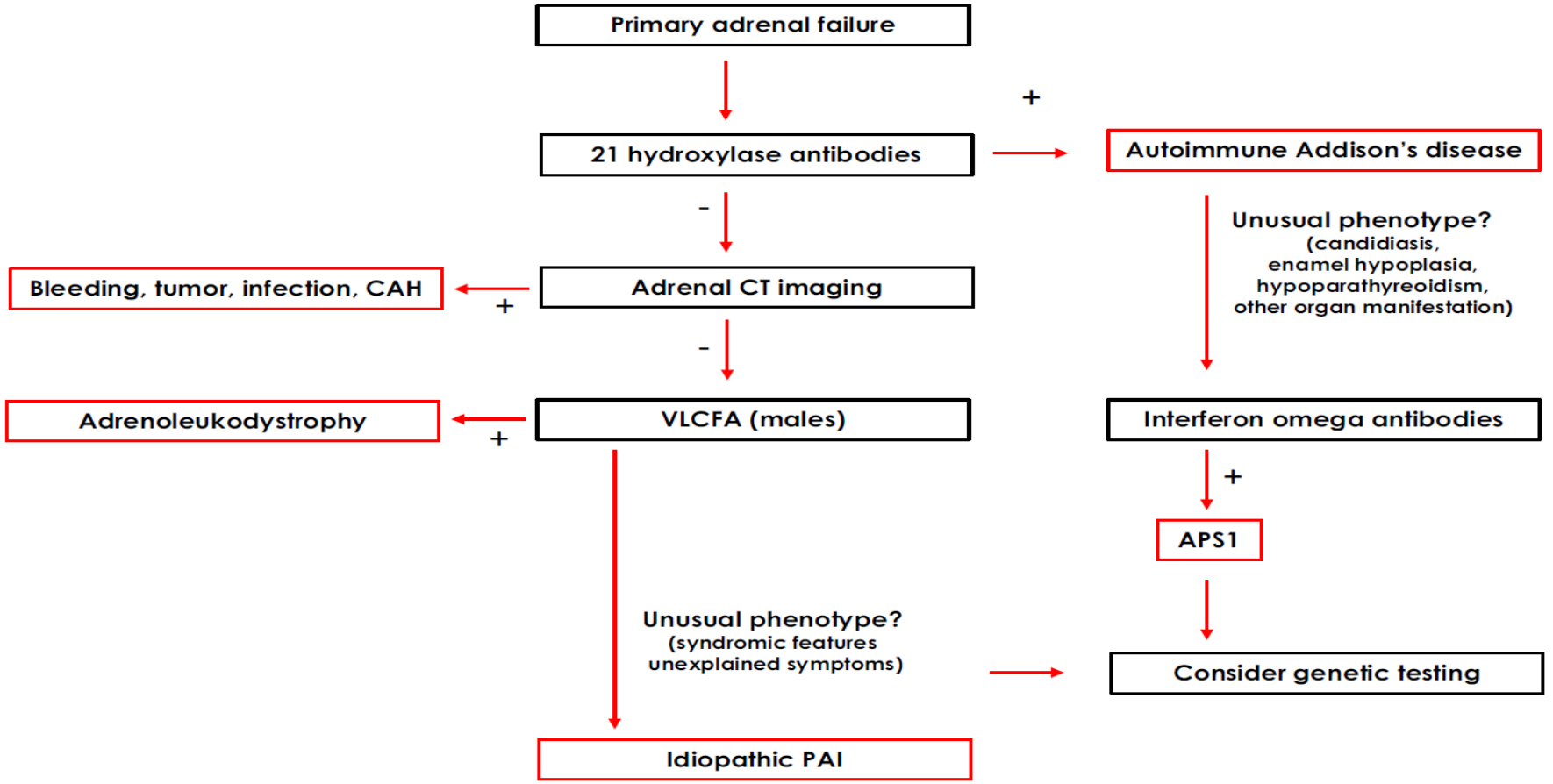


Diagnostic approach to suspected chronic adrenal insufficiency



Uptodate oct 2023

Diagnostic algorithm for etiological diagnosis in primary adrenal insufficiency.



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https://doi.org/10.1210/clinem/dgad402

Treatment of adrenal insufficiency in adults

Emergency management of adrenal crisis

- Adrenal insufficiency should be ruled out in any acutely ill patient with signs or symptoms potentially suggestive of acute adrenal insufficiency
- Assess blood pressure and fluid balance status; if clinically feasible, measure blood pressure from supine to standing to check for postural drop
- Assess patient drug history; determine whether there has been glucocorticoid use
- Perform appropriate blood tests: Sodium, potassium, urea, and creatinine; full blood counts; thyroid-stimulating hormone and free thyroxine; paired serum cortisol and plasma ACTH

http://www.endocrineconnections.org

Anaesthesia 2020, 75, 654–663

Emergency management of adrenal crisis

- If the patient is hemodynamically stable, consider performing a short Synacthen test (serum cortisol at baseline and 30 min after intravenous injection of 250 µg ACTH $_{1–24}$)
- Serum/plasma aldosterone and plasma renin
- Diagnostic measures should never delay prompt treatment of a suspected adrenal crisis
- Administer hydrocortisone: Immediate bolus injection of 100 mg hydrocortisone intravenously or intramuscularly followed by continuous intravenous infusion of 200 mg hydrocortisone per 24 hours (alternatively, 50 mg hydrocortisone per intravenous or intramuscular injection every 6 h)

http://www.endocrineconnections.org
Anaesthesia 2020, 75, 654–663

Emergency management of adrenal crisis

- Rehydrate with rapid intravenous infusion of 1000 mL of isotonic saline infusion within the first hour, followed by further intravenous rehydration as required (usually 4-6 L in 24 h; monitor for fluid overload in case of renal impairment and in elderly patients)
- Investigate of the underlying cause of the disease, including the diagnosis of primary versus secondary adrenal insufficiency
- Tapering of hydrocortisone can be started after clinical recovery guided by an endocrinologist; in patients with primary adrenal insufficiency, mineralocorticoid replacement must be initiated (starting dose 100 µg fludrocortisone once daily) as soon as the daily glucocorticoid dose is below 50 mg of hydrocortisone every 24 hours

http://www.endocrineconnections.org
Anaesthesia 2020, 75, 654–663

Adrenal hormone replacement therapy in adults with adrenal insufficiency

- Glucocorticoid replacement

➢ Hydrocortisone 15 to 25 mg orally in two or three divided doses (largest dose in morning upon awakening 10/5/2.5) **or**
➢ Prednisone 5 mg (range: 2.5 to 7.5 mg) orally at bedtime; **or**
➢ Dexamethasone 0.75 mg (range: 0.25 to 0.75 mg) orally at bedtime
➢ Monitor clinical symptoms and morning plasma ACTH.

- Mineralocorticoid replacement

➢ Fludrocortisone 0.1 mg (range: 0.05 to 0.2 mg) orally.
➢ Liberal salt intake.
➢ Monitor lying and standing blood pressure and pulse, edema, serum potassium, and plasma renin activity.

- Androgen replacement

➢ Dehydroepiandrosterone (DHEA) initially 25 to 50 mg orally (only in women with impaired mood or sense of well-being despite optimal glucocorticoid and mineralocorticoid replacement).

Glucocorticoid therapy monitoring

- Glucocorticoid replacement therapy is monitored through clinical assessments rather than biochemical tests.
- Patients should be assessed at least once every three months early after diagnosis and during dose titration and at least once annually after a stable replacement regimen is established.
- Routine clinical assessments include measurement of blood pressure, heart rate, and body weight, as well as detailed symptom queries.

Clin Endocrinol (Oxf). 1997;46(3):255.

Annual assessment

- Clinical – Be mindful for signs of glucocorticoid excess, eg weight gain, hypertension or poor glycemic control. Hypertension and edema may suggest excessive mineralocorticoid replacement, whereas postural hypotension and salt craving suggest insufficient treatment. Timing of glucocorticoid doses may need varying if patients describe symptoms of insufficiency at certain points in the day.
- Biochemical – Cortisol day curves (salivary cortisone or serum cortisol) can be used to assess glucocorticoid adequacy if there are concerns about frequent crisis or symptoms despite adequate dosing regimes. Patients who have autoimmune adrenal disease should be screened for other manifestations of commonly associated autoimmune diseases.
- Prevention – annual influenza vaccination should be offered and pneumococcal vaccination for those age >60.

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Dose adjustments for increased salt losses / primary hypertension

- Vigorous exercise or warm climates

➢ In prolonged exercise (eg, long-distance running or cycling) may need to increase the fludrocortisone dose .

➢ During the summer or in warmer climates(temperatures above approximately 29°Celsius) fludrocortisone dose may need to be increased **by 50 to 100** percent.

➢ Alternatively, **salt tablets** may be used to provide an additional 1 to 2 g sodium daily.

- Hypertension

➢ Dietary sodium restriction and reduced dose of fludrocortisone

➢ Mineralocorticoid therapy usually cannot be discontinued without risking sodium depletion.

➢ Diuretics, eplerenone, or spironolactone should **not** be used.

J Endocrinol Invest. 1991;14(2):87.

Mineralocorticoid therapy monitoring

- Mineralocorticoid therapy monitoring — In patients with mineralocorticoid deficiency, both clinical and biochemical assessments are needed to assess the adequacy of mineralocorticoid replacement therapy. These assessments are performed **at least every one to three months** during treatment initiation or dose adjustments and at least annually in individuals on stable replacement regimens.
- Clinical assessment – Clinical monitoring includes queries about symptoms of fatigue, lightheadedness, nausea, muscle cramping, and salt craving. Routine monitoring also includes measurement of supine and upright blood pressure and heart rate to assess for postural hypotension. Hypertension and edema are signs of excessive mineralocorticoid replacement.

Clin Endocrinol (Oxf). 1996;45(5):529.

Sick day rules

- For moderate illness (eg fever, infection requiring antibiotics, surgical procedure under local anaesthetic), usual oral steroid dose can be doubled up. In patients with suspected or proven COVID-19 infection, high doses of gluccocorticoid supplementation (equivalent to hydrocortisone 20 mg four times daily) should be used.
- To cover severe illness, eg persistent vomiting, pneumonia, trauma or acute surgery, patients should receive an initial bolus of 100 mg IV hydrocortisone followed by 50 mg (IM or IV) hydrocortisone 6-hourly or 200 mg / 24 hour IV infusion until resolution of the illness.
- For moderate elective procedures or investigations, eg endoscopy or angiography, patients should receive a single dose of 100 mg hydrocortisone before the procedure.

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Mineralocorticoid therapy monitoring

- **Biochemical assessment** – Biochemical monitoring includes measurement of the serum sodium, potassium, and creatinine concentrations and PRA. We adjust the fludrocortisone dose to lower the PRA to the upper reference range .
- If direct renin concentration (DRC) is measured instead of PRA, targeting a DRC that is within the reference range or mildly elevated is reasonable.
- Remeasure PRA three months after initiating fludrocortisone therapy or sooner if patients report any signs or symptoms of under- or overtreatment.
- Titrate the fludrocortisone dose in 0.05 mg increments as needed to achieve the target PRA.
- Once a stable fludrocortisone dose is achieved, measure PRA annually in all patients and whenever a patient develops signs or symptoms of mineralocorticoid deficiency or excess.
- Normal morning PRA for seated, healthy individuals with a typical dietary sodium intake ranges from approximately 1 to 4 ng/mL per hour (0.8 to 3 nmol/L per hour).

Clin Endocrinol (Oxf). 1996;45(5):529.

Glucocorticoid supplement for surgical stress:

- Minor (eg, herniorrhaphy): hydrocortisone 25 mg IV (or equivalent) on day of procedure
- Moderate (eg, orthopedic surgery): hydrocortisone 50 to 75 mg IV (or equivalent) on day of surgery and postoperative day 1
- Major (eg, cardiac bypass): hydrocortisone 100 to 150 mg IV (or equivalent) in two or three divided doses on day of surgery and postoperative days 1 and 2
- Then return to usual daily glucocorticoid dose.
- General anesthesia or IV sedation should not be performed in the office setting.

Pregnancy and labor

➢**Pregnancy**

•**Glucocorticoid therapy** – For pregnant individuals, hydrocortisone is preferred .

- In the third trimester, most patients require an increase in the hydrocortisone dose of approximately 20 to 40 percent. This adjustment can be made empirically at pregnancy weeks 20 to 24 or as needed on the basis of clinical course.
- **Mineralocorticoid therapy** – Dose adjustments for mineralocorticoid therapy are generally not needed during pregnancy.
- A plasma renin activity in the upper half of the reference range for pregnant individuals is a reasonable target.

Suggested Plan for Steroid Replacement in Patients Withdrawing From Chronic Corticosteroid Therapy

Pred Dose (mg/day)	Duration of Glucocorticoid Treatment			
	≤3 wk [a]		>3 wk	
≥7.5	Can stop	↓ rapidly (e.g., 2.5 mg q3-4d)		
		THEN		
5–7.5	Can stop	↓ 1 mg q2-4 wk	OR	Convert 5 mg pred to 20 mg HC, then ↓ 2.5 mg/wk to 10 mg/day
		THEN		THEN
<5	Can stop	↓ 1 mg q2-4 wk		After 2-3 mo HC 10 mg/day, administer SST/ITT: Pass → Withdraw Fail → Continue

Thanks for your attention