



Cushing's Syndrome

Exclude the steroids first, confirm with two tests, then let ACTH split the causes · in that order

Exogenous first
always

⚠ STEP ZERO: EXOGENOUS GLUCOCORTICOIDS ARE BY FAR THE COMMONEST CAUSE

Take a full steroid history before ordering a single test. Ask about oral, inhaled, topical, intra-articular and intranasal preparations, and about **over-the-counter creams, herbal and imported remedies**, which frequently contain undeclared steroid. **The giveaway is a suppressed ACTH with low cortisol on testing**, since the exogenous steroid suppresses the whole axis and is usually not measured by the cortisol assay. Working up an iatrogenic case as if it were a tumor is the classic wasted month.

WHO TO TEST *the features that actually discriminate*

DISCRIMINATING FEATURES

Proximal myopathy, wide purple striae over 1 cm, easy bruising and facial plethora. These carry the most weight because they are uncommon in simple obesity.

NON-DISCRIMINATING

Weight gain, central obesity, hypertension, diabetes, depression and menstrual irregularity are all **common in the general population**, so they raise suspicion but do not distinguish. **Test when features cluster, are progressive, or are unusual for the patient's age.**

ALSO TEST

Unexplained osteoporosis or fragility fracture in a young patient, resistant hypertension with hypokalemia, an **adrenal incidentaloma**, and children with weight gain plus falling height velocity, which is a nearly specific combination.

STEP 1: CONFIRM THE CORTISOL EXCESS *use at least two of the three, and repeat abnormal results*

Test	How it works and what trips it up
1 mg overnight dexamethasone suppression	Dexamethasone at 11 p.m., cortisol at 8 a.m. Failure to suppress is abnormal. False positives with anything that induces CYP3A4 (phenytoin, carbamazepine, rifampin), and with estrogen or pregnancy , which raise cortisol-binding globulin and therefore total cortisol
Late-night salivary cortisol	Targets the loss of the normal nocturnal nadir , which is the earliest biochemical abnormality. Convenient and repeatable at home. Unreliable in shift workers and in anyone with a disrupted sleep-wake cycle
24-hour urinary free cortisol	Measures total daily output. Collect at least twice , and check the creatinine to confirm the collection was complete. High fluid intake raises it falsely , and it misses mild disease
⚠ Exclude pseudo-Cushing	Severe obesity, poorly controlled diabetes, depression, chronic alcohol use, and physiological stress all produce mild biochemical hypercortisolism. This is why two concordant abnormal tests are required , and why borderline results should be repeated rather than escalated straight to imaging

STEP 2: ACTH SPLITS IT *only after the excess is confirmed, never before*

ACTH	What it means, and what to do next
SUPPRESSED <i>ACTH-independent</i>	The adrenal is the problem. Adrenal adenoma, carcinoma, or bilateral hyperplasia. Go to adrenal CT. Suspect carcinoma with a large, heterogeneous mass, rapid onset, or virilization alongside the cortisol excess
NORMAL or ELEVATED <i>ACTH-dependent</i>	Pituitary or ectopic. Pituitary disease, Cushing's DISEASE , accounts for the large majority. Next step is pituitary MRI , plus high-dose dexamethasone suppression and CRH testing to help separate the two
Pituitary versus ectopic	Pituitary tumors usually retain some feedback , so they suppress on high-dose dexamethasone and respond to CRH; ectopic sources usually do neither. Ectopic disease is suggested by rapid onset, severe hypokalemia and metabolic alkalosis, marked hyperpigmentation, and weight loss rather than gain , most often from a small cell lung cancer or a bronchial carcinoid
⚠ Inferior petrosal sinus sampling	The tie-breaker, and it is needed more often than people expect. Pituitary microadenomas are frequently invisible on MRI, and incidental pituitary lesions are common in healthy people , so an MRI finding alone can mislead in both directions. IPSS is indicated when the MRI shows no clear adenoma, or when the biochemistry and imaging disagree

SCREEN AND TREAT THE DAMAGE *these do not all reverse, and some are urgent*

Complication	What to do about it
⚠ Venous thromboembolism	Cortisol excess creates a genuinely prothrombotic state , and the risk is highest around surgery. This is the complication most often overlooked: ensure thromboprophylaxis is considered perioperatively and have a low threshold for investigating symptoms
Diabetes and hypertension	Check HbA1c and blood pressure at diagnosis and treat actively. Both often improve after cure but frequently do not resolve , so do not defer treatment while awaiting surgery
Osteoporosis	DEXA at diagnosis. Bone loss can be rapid and fractures occur at higher bone density than usual, so treat on the basis of the whole picture rather than the T-score alone. Ensure calcium and vitamin D
Hypokalemia and alkalosis	Marked hypokalemia points toward ectopic ACTH , where very high cortisol overwhelms the enzyme that normally protects the mineralocorticoid receptor. Replace potassium and consider spironolactone
Infection	These patients are functionally immunosuppressed and present atypically with blunted signs. Consider PJP prophylaxis in severe hypercortisolism, and treat suspected infection promptly rather than observing

TREATMENT & PEARLS

- **Surgery is the definitive treatment:** transsphenoidal resection for Cushing's disease, adrenalectomy for an adrenal source, and resection of the tumor in ectopic disease. **Medical therapy** (steroidogenesis inhibitors such as osilodrostat, metyrapone or ketoconazole, or a pituitary-directed agent) is used to control severe hypercortisolism before surgery, after failed surgery, or while a source is located.
- **Expect adrenal insufficiency after successful surgery, and treat it as a sign of cure.** The contralateral adrenal is suppressed, so patients need **glucocorticoid replacement with a slow taper over many months**, sick-day rules and an emergency plan. **Stopping replacement too early causes an adrenal crisis.**
- **The complications need treating in their own right and do not all reverse:** diabetes, hypertension, osteoporosis, and a **markedly increased venous thromboembolism risk**, which is easy to overlook perioperatively. **Infection risk is raised while immunosuppressed by the cortisol**, and presentations are blunted.
- **Psychiatric symptoms are part of the disease, not a reaction to it.** Depression, emotional lability, insomnia and occasionally psychosis are common, can precede the physical features, and usually improve after treatment though not always completely. **Warn patients that recovery takes many months**, since expecting to feel well immediately after surgery leads to considerable distress.

