Cushing's syndrome and adrenal insufficiency
Clinician expectations

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Main Challenges

- Rare but important
- Mild forms (unrecognized)
- Cyclic forms (may be missed)
- Incidentaloma
- Too many differentials, psudo-cushing
- Too many tests , needs retests (lab or imaging)
- Dynamic plus static tests needs hospital admission, time consuming and costly
- Close contact and coordination with lab (unites, dates…….)

Etiology of Cushing

	Proportion (%)	Age (peak)	Female:male	Features
ACTH-dependent	70–80	..	..	..
Cushing's disease	60–70	..	..	..
Corticotroph adenoma	60–70	3rd–4th decades	3–5:1	Roughly 50% non-visible on MRI
Corticotroph hyperplasia	Very rare	..	..	..
Ectopic ACTH*	5–10	..	..	..
Malignant neuroendocrine tumours	About 4	5th–6th decades	0·6–1:1	Might have very high ACTH
Benign neuroendocrine tumours	About 6	3rd–4th decades	..	Might respond to dexamethasone, CRH, desmopressin
Occult neuroendocrine tumours	About 2	..	..	..
Ectopic CRH	Very rare	..	..	Causes pituitary corticotroph hyperplasia
ACTH-independent	20–30	..	..	..
Unilateral adrenal	..	..	..	..
Adenoma	10–22	4th–5th decades	4–8:1	Most pure cortisol secretion
Carcinoma	5–7	1st, 5th–6th decades	1·5–3:1	Mixed cortisol and androgen frequent
Bilateral adrenal	1–2	..	..	..
Bilateral macronodular adrenal hyperplasia†	<2	5th–6th decades	2–3:1	Modest cortisol secretion compared with size; raised steroid precursors; might have combined androgen and mineralocorticoid cosecretion
Aberrant G-protein-coupled receptors	..	..	..	..
Autocrine ACTH production	..	..	..	..
Sporadic or familial (*ARMC5*)	..	..	..	..
Bilateral micronodular adrenal hyperplasias	<2	..	..	Adrenal size often normal
Primary pigmented nodular adrenocortical disease	Rare	1st–3rd decades	0·5:1 <12 years 2:1 >12 years	Frequent paradoxical increase of urine free cortisol with Liddle's oral dexamethasone suppression test
Isolated or familial with Carney complex	Rare	1st–3rd decades	..	..
Isolated micronodular adrenocortical disease	Very rare	Infants	..	Non-pigmented adrenal micronodules
Primary bimorphic adrenocortical disease	Very rare	Infants	..	..
McCune-Albright syndrome	Rare	Infants (<6 months)	1:1	Internodular adrenal atrophy
Bilateral adenomas or carcinomas	Rare	4th–5th decades	2–4:1	..

ACTH=adrenocorticotropic hormone. CRH=corticotropin-releasing hormone.* Most frequent sources of ectopic ACTH syndromes are small cell lung carcinoma and neuroendocrine tumours of lung, thymus, and pancreas. Less frequent causes include medullary thyroid carcinoma, gastrinoma, phaeochromocytoma, prostate carcinoma, and several others. †In bilateral macronodular adrenal hyperplasia tissues, autocrine and paracrine ACTH might be produced and contribute to cortisol secretion. If confirmed by in-vivo studies, the ACTH-independent classification will need to be modified in the future.

***Table 1*: Causes of endogenous Cushing's syndrome**

Causes Of Cushing's syndrome

Causes of spontaneous Cushing's syndrome.

ACTH-dependent

Pituitary ACTH over-secretion

- Cushing's disease 60–70%
- CRH-secreting tumours (rare)

Non-pituitary ACTH over-secretion

- Ectopic ACTH syndrome 5–10%

ACTH-independent

Unilateral adrenocortical tumour

- Adrenocortical adenoma 10–15%
- Adrenocortical carcinoma 10–15%

Bilateral adrenocortical involvement

- Primary pigmented nodular
- Adrenocortical dysplasia (rare)
- ACTH-independent bilateral macronodular adrenocortical hyperplasia (rare)

Hypercortisolic states without Cushing's syndrome

- Various pathological or physiological conditions may be associated with biochemical, and sometimes clinical, evidence of endogenous glucocorticoid excess.

- In these situations, increased cortisol production is thought to be driven by pituitary ACTH oversecretion, secondary to a CNS disorder or to an appropriate adaptive reaction.

Hypercortisolic states without Cushing's syndrome

This functional hypercortisolic state '("Pseudo-Cushing') is usually:

1. mild and transient
2. regressing with its cause
3. thus is not classically regarded as a cause of genuine Cushing's syndrome.

Hypercortisolism

TABLE 2. Conditions associated with hypercortisolism in the absence of Cushing's syndrome[a]

Conditions
Some clinical features of Cushing's syndrome may be present
Pregnancy
Depression and other psychiatric conditions
Alcohol dependence
Glucocorticoid resistance
Morbid obesity
Poorly controlled diabetes mellitus
Unlikely to have any clinical features of Cushing's syndrome
Physical stress (hospitalization, surgery, pain)
Malnutrition, anorexia nervosa
Intense chronic exercise
Hypothalamic amenorrhea
CBG excess (increased serum but not urine cortisol)

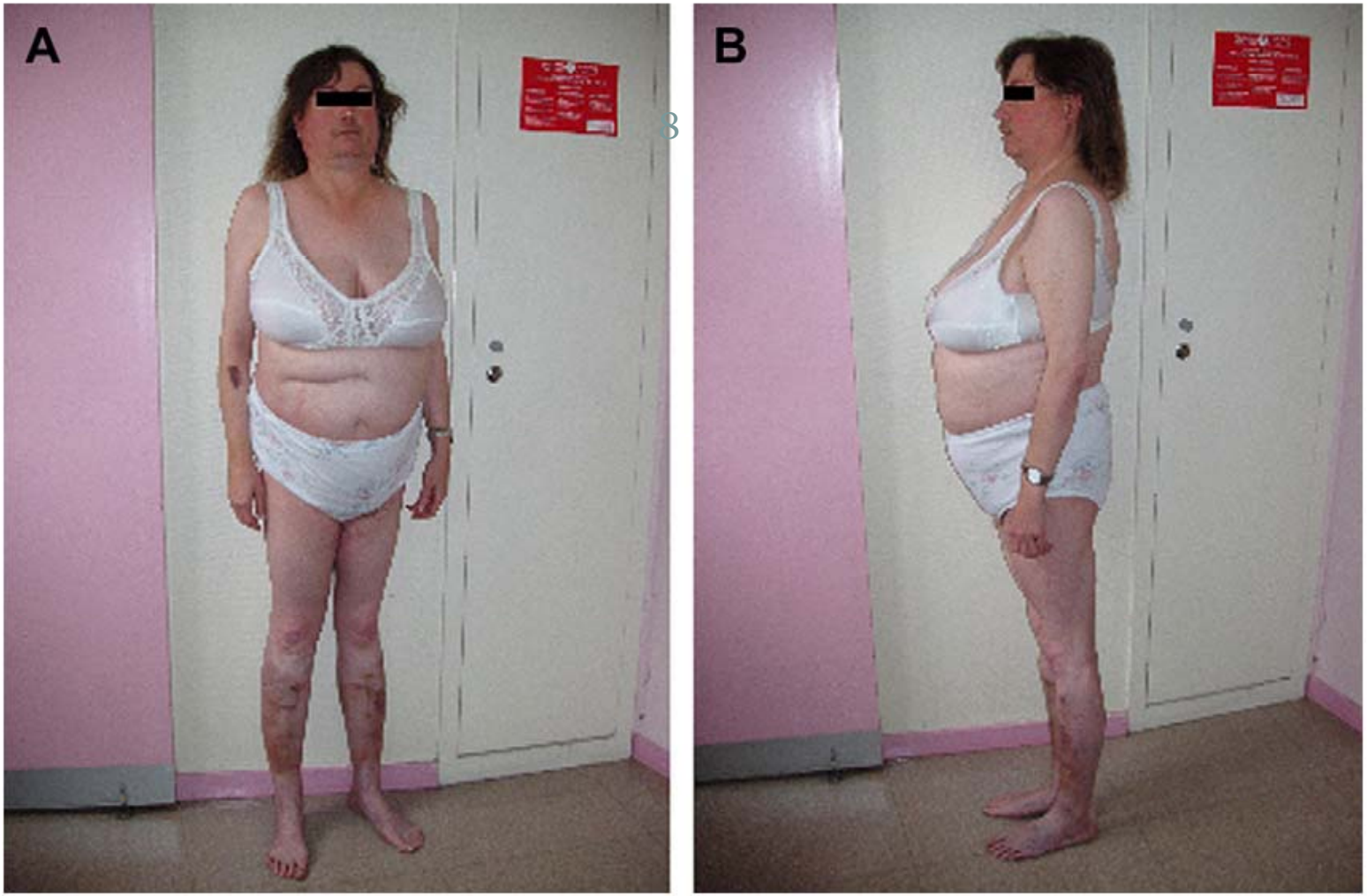

Fig. 1. (A & B) Typical aspect of a patient with Cushing's syndrome: centripetal fat depositing with truncal obesity contrasting with the muscular atrophy of the thighs and legs (Personal collection).

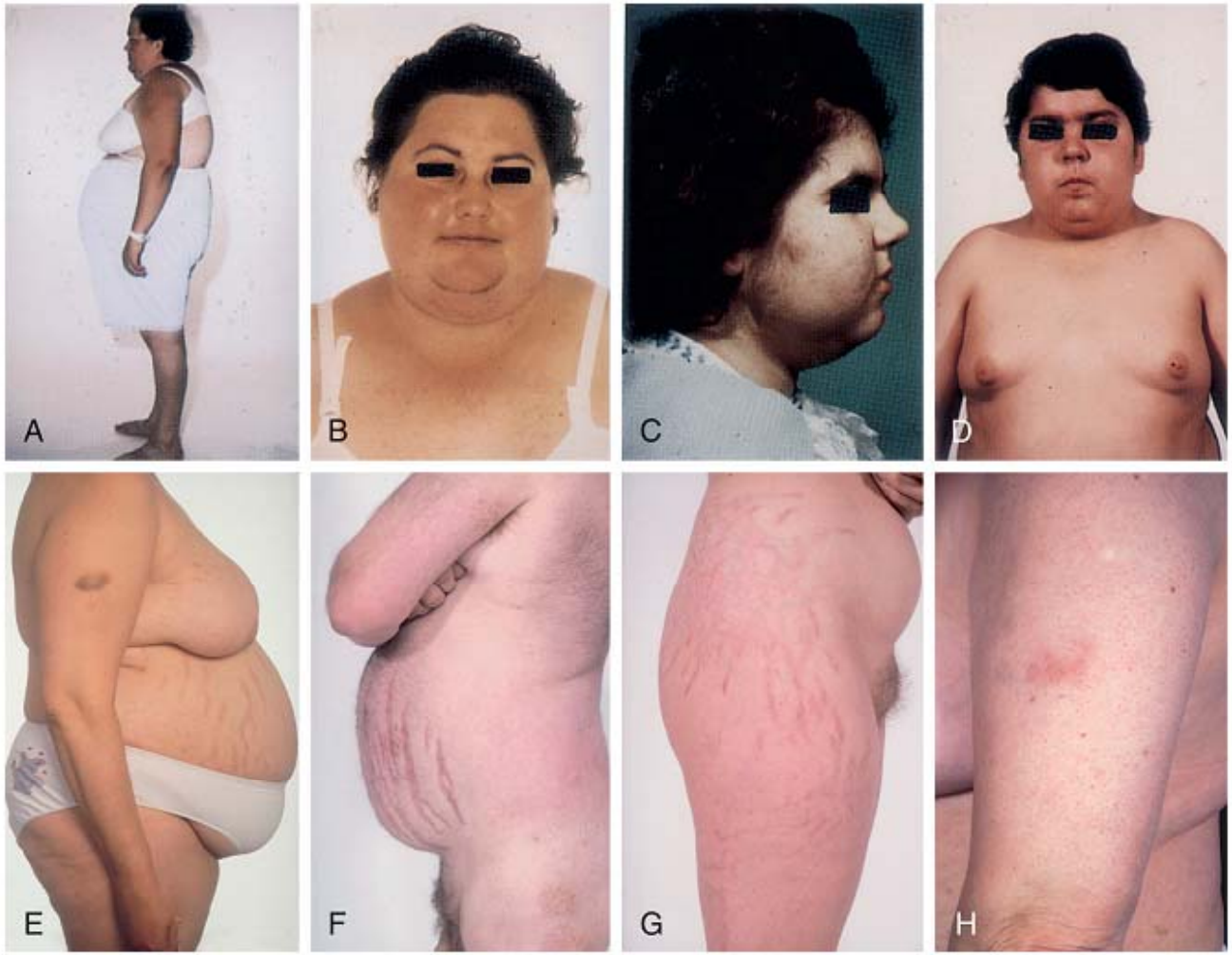

Figure 15-16 Clinical features of Cushing syndrome. **A,** Centripetal and some generalized obesity and dorsal kyphosis in a 30-year-old woman with Cushing disease. **B,** Same patient as in **A,** showing moon facies, plethora, hirsutism, and enlarged supraclavicular fat pads. **C,** Facial rounding, hirsutism, and acne in a 14-year-old girl with Cushing disease. **D,** Central and generalized obesity and moon facies in a 14-year-old boy with Cushing disease. **E** and **F,** Typical centripetal obesity with livid abdominal striae seen in a 41-year-old woman (**E**) and a 40-year-old man (**F**) with Cushing syndrome. **G,** Striae in a 24-year-old patient with congenital adrenal hyperplasia treated with excessive doses of dexamethasone as replacement therapy. **H,** Typical bruising and thin skin of a patient with Cushing syndrome. In this case, the bruising occurred without obvious injury.

values

Risk of false-positive test results is high

- Because of the rarity of Cushing's syndrome
- High prevalence of conditions such as DM, obesity, and depression
- Limitations of the screening tests

values

- False-positive results, with their attendant costs, are reduced if case detection is limited to individuals with an increased pretest probability of having the disorder.

- The subsequent testing, labeling, and treatment may harm individuals with false-positive results and distract attention from the treatment of the conditions that prompted testing.

Diagnosis of Cushing's syndrome
Who should be tested

- Obtain a thorough drug history to exclude **exogenous glucocorticoid** exposure leading to iatrogenic Cushing's syndrome before conducting biochemical testing.

Diagnosis of Cushing's syndrome
Who should be tested

- We recommend testing for Cushing's syndrome in the following groups:

1-Patients with unusual features for age (*osteoporosis*, HTN)

2-Patients with multiple and progressive features, particularly those that are more predictive of Cushing's syndrome .

Diagnosis of Cushing's syndrome
Who should be tested

3- Children with decreasing height percentile and increasing weight

4-Patients with adrenal incidentaloma compatible with adenoma.

We recommend against widespread testing for Cushing's syndrome in any other patient group.

Discriminatory findings

- Cushing's syndrome is more likely to be present when a large number of signs and symptoms, especially those with high discriminatory index
- Myopathy
- Plethora
- Red striae
- Easy bruising
- Thin skin in the young

Initial testing

we recommend one of the following tests :

1- Urine free cortisol (UFC; at least 2 measurements)

2- Late-night salivary cortisol (2 measurements)

Initial testing

3- 1-mg overnight dexamethasone suppression test (DST)

4- Longer low-dose DST (2 mg/d for 48 h)

Initial testing

- In individuals with at least one abnormal test result (for whom the results could be falsely positive or indicate Cushing's syndrome), we recommend further evaluation by an endocrinologist to confirm or exclude the diagnosis

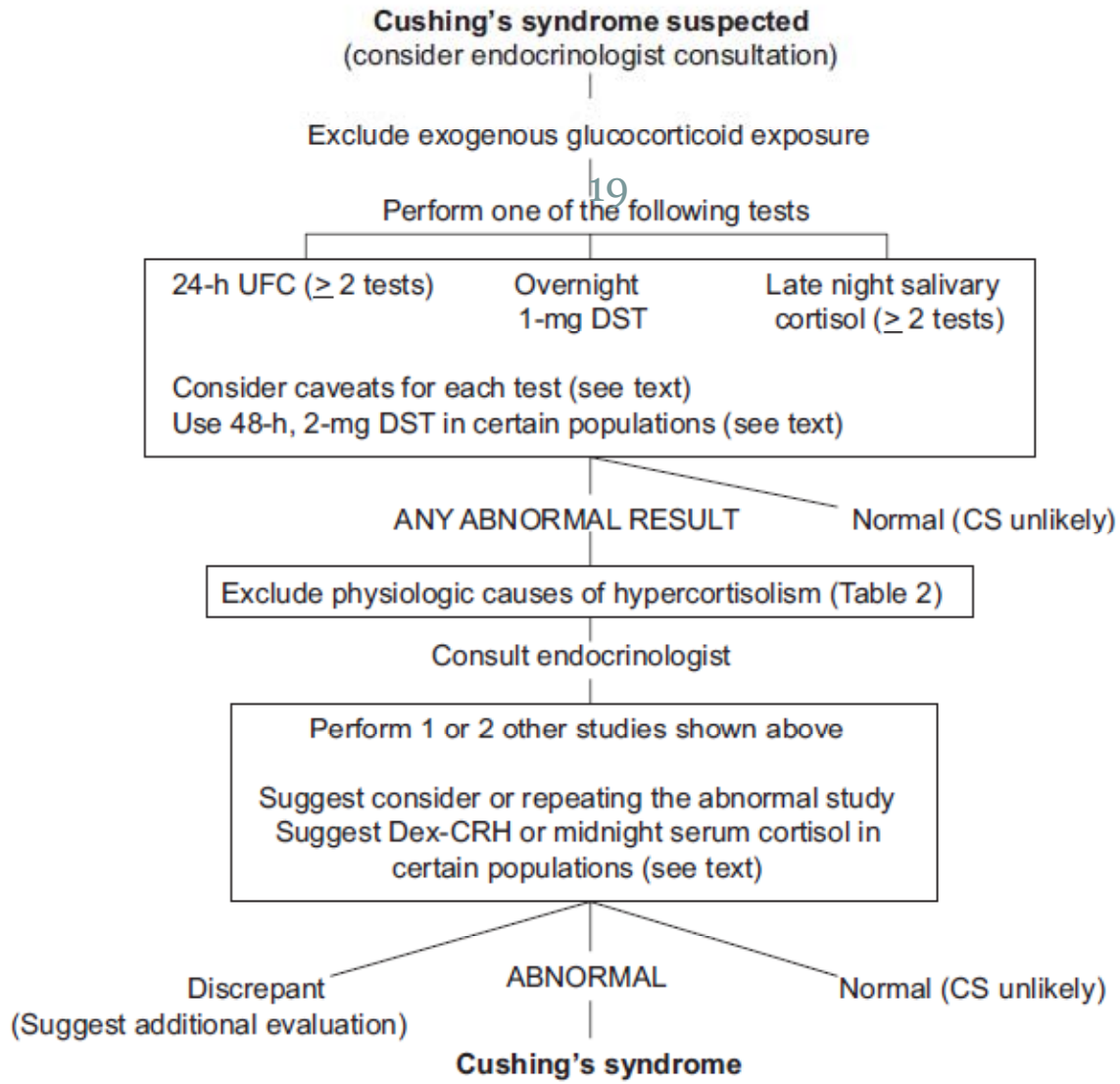

FIG. 1. Algorithm for testing patients suspected of having Cushing's syndrome (CS). All statements are recommendations except for those prefaced by suggest. Diagnostic criteria that suggest Cushing's syndrome are UFC greater than the normal range for the assay, serum cortisol greater than 1.8 μg/dl (50 nmol/liter) after 1 mg dexamethasone (1-mg DST), and late-night salivary cortisol greater than 145 ng/dl (4 nmol/liter).

Remarks for all tests

- Antibody-based immunoassays such as RIA and ELISA can be affected by cross-reactivity **with cortisol metabolites and synthetic glucocorticoids.**

- In contrast, structurally based assays such as **HPLC and tandem mass spectrometry** (LC-MS/MS) do not pose this problem and are being used with increasing frequency

Remarks for all tests

- There are also drugs **(carbamazepine and fenofibrate)** that may interfere with some of these chromatographic methods (next Table), thereby causing falsely elevated values

TABLE 3. Selected drugs that may interfere with the evaluation of tests for the diagnosis of Cushing's syndrome[a]

22Drugs
Drugs that accelerate dexamethasone metabolism by induction of CYP 3A4
Phenobarbital
Phenytoin
Carbamazepine
Primidone
Rifampin
Rifapentine
Ethosuximide
Pioglitazone
Drugs that impair dexamethasone metabolism by inhibition of CYP 3A4
Aprepitant/fosaprepitant
Itraconazole
Ritonavir
Fluoxetine
Diltiazem
Cimetidine
Drugs that increase CBG and may falsely elevate cortisol results
Estrogens
Mitotane
Drugs that increase UFC results
Carbamazepine (increase)
Fenofibrate (increase if measured by HPLC)
Some synthetic glucocorticoids (immunoassays)
Drugs that inhibit 11β-HSD2 (licorice, carbenoxolone)

1-Remarks for all tests

- Upper limits of normal are much lower with HPLC or LC-MS/MS than in antibody-based assays.

- For example, urine cortisol values obtained using HPLC may be as low as 40% of the value measured by RIA

1-Remarks for all tests

- Estrogens increase the cortisol-binding globulin (CBG) in the circulation.
- Because serum assays measure total cortisol, false-positive rates for the overnight DST are seen in 50% of women taking the OCP.

1-Remarks for all tests

- Wherever possible, estrogen-containing drugs should be withdrawn for 6 wk before testing or retesting.

- Decreases in CBG or albumin, which occur in the critically ill or nephrotic patient, are associated with decreased serum cortisol .

1-Remarks for all tests

- Because the hypercortisolism of Cushing's syndrome can be variable, we recommend that **at least two measurements of urine or salivary cortisol be obtained.**

- This strategy **increases confidence** in the test results if consistently normal or abnormal results are obtained.

2-Remarks for dexamethasone tests

- Variable absorption and metabolism of dexamethasone may influence the result of both the overnight 1-mg DST and the 48-h, 2 mg/d test.

- Drugs such as phenytoin, phenobarbitone, carbamazepine, rifampicin, and alcohol induce hepatic enzymatic clearance of dexamethasone, mediated through CYP3 A4, thereby reducing plasma dexamethasone.

2-Remarks for dexamethasone tests

- Conversely, dexamethasone clearance may be reduced in patients with liver and/or renal failure.
- Dexamethasone levels show interindividual variation, however, even in healthy individuals on no medication

Evidence for use of UFC

- UFC provides an integrated assessment of cortisol secretion over a 24-h period.
- It measures the cortisol that is not bound to CBG, which is filtered by the kidney unchanged.
- Therefore, unlike serum cortisol, which measures both CBG-bound and free hormone, UFC is not affected by conditions and medications that alter CBG.

Evidence for use of UFC

- For example, healthy women taking oral estrogen may have increased CBG, and therefore high serum cortisol , but their UFC remains normal.

- Because cortisol production is increased in Cushing's syndrome, the amount of unbound hormone is higher, resulting in elevated UFC values

cutoffs

- As with any other test, sensitivity and specificity of UFC are subject to the cutoffs selected.
- When the assay upper limit of normal is used as a criterion, the overall evidence supports the diagnostic accuracy of UFC in adults suspected of having Cushing's syndrome .
- Sensitivity for Cushing's syndrome in pediatric patients is high (89%)

Evidence for use of UFC

- To achieve the goal of high sensitivity, we recommend using the upper limit of normal for the particular assay as the criterion for a positive test

- provided the creatinine shows that the collection is complete and there is not excessive volume

False positive UFC

At the recommended cutoff point, false-positive elevations of UFC may be seen in several conditions.

1- High fluid intake (5 liters/d) significantly increases UFC .

2- Any physiological or pathological condition that increases cortisol production raises UFC.

- Therefore, in these conditions a normal result is more reliable than an abnormal one.

False negative UFC

- At the recommended cutoff point, false-negative results of urine cortisol collections also may occur.
- Because UFC reflects renal filtration, values are significantly lower in patients with moderate to severe renal impairment.

False negative UFC

1-A falsely low UFC can occur when **creatinine clearance <60 ml/min**, and UFC levels fall linearly with more severe renal failure.

2- UFC can be normal if a patient has **cyclic disease** and collects urine when the disease is inactive.

3- It may be normal in some patients with **mild Cushing's syndrome**, in whom salivary cortisol may be more useful

Remarks for UFC
Sample collection and instructions

- It is important to ensure that patients provide a complete 24-h urine collection with appropriate total volume and urinary creatinine levels

Remarks for UFC

- Patients should be instructed not to drink excessive amounts of fluid
- avoid the use of any glucocorticoid preparations, including steroid-containing skin or hemorrhoid creams, during the collection.
- Because UFC levels in a patient with Cushing's syndrome are variable
- At least two collections should be performed, particularly in children in whom reproducibility can be low.

Evidence for late-night salivary cortisol

- In healthy individuals with stable conventional sleep-wake cycles, the level of serum cortisol begins to rise at 0300–0400 h
- Reaches a peak at 0700–0900 h
- Falls for the rest of the day to very low levels when the person is unstressed and asleep at midnight .

Evidence for late-night salivary cortisol

- The loss of circadian rhythm with absence of a late-night cortisol nadir is a consistent biochemical abnormality in patients with Cushing's syndrome.

- This difference in physiology forms the basis for measurement of a midnight serum or late-night salivary cortisol.

Evidence for late-night salivary cortisol

1-Biologically active free cortisol in blood is in equilibrium with cortisol in the saliva

2- Concentration of salivary cortisol does not appear to be affected by the rate of saliva production.

3- Increase in blood cortisol is reflected by a change in the salivary cortisol within a few minutes .

Evidence for late-night salivary cortisol

- Various methods have been used to measure cortisol in the saliva
- Resulting in different reference ranges and yielding differences in sensitivity and specificity .
- The best-validated assays used in the US to measure salivary cortisol are an ELISA and an assay performed by LC-MS/MS .

Evidence for late-night salivary cortisol

- When these two assay techniques are used, normal subjects usually have salivary cortisol at bedtime, or between 2300 and 2400 h, of <145 ng/dl (4 nmol/liter).

Evidence for late-night salivary cortisol

- Using a variety of assays and diagnostic criteria, late-night salivary cortisol
- 92–100%sensitivity
- 93–100% specificity for the diagnosis of Cushing's syndrome.

- Overall, the evidence in adults suggests that the accuracy of this test is similar to that of UFC.

Evidence for late-night salivary cortisol

It is important to note that the circadian rhythmis blunted in many patients with

- depressive illness
- shift workers
- may be absent in the critically ill.

- In a study of men aged 60 yr or older, Liu et al. reported that 20% of all participants and 40% of diabetic hypertensive subjects had at least one elevated late-night salivary cortisol measurement.

Remarks for late-night salivary cortisol

- Most clinicians using the late-night salivary cortisol test ask patients to collect a saliva sample on two separate evenings between 2300 and 2400 h.
- Saliva is collected either by passive drooling into a plastic tube or by placing a cotton pledget (salivette) in the mouth and chewing for 1–2min.
- The sample is stable at room or refrigerator temperature for several weeks and can be mailed to a reference laboratory.
- Reports show good correlation between salivary and simultaneous serum cortisol values in healthy volunteers.

Remarks for late-night salivary cortisol

- Several factors that affect the salivary cortisol test should be considered when evaluating the results.
- The salivary glands express 11-hydroxysteroid dehydrogenase type 2 (11-HSD2), which converts the biologically active cortisol to inactive cortisone

Remarks for late-night salivary cortisol

- It is theoretically possible that individuals using licorice or chewing tobacco (both of which contain the 11-hydroxysteroid dehydrogenase type 2 inhibitor glycyrrhizic acid) may have a falsely elevated late-night salivary cortisol.

- Patients who smoke cigarettes also have been shown to have higher late-night salivary cortisol measurements than do nonsmokers

Remarks for late-night salivary cortisol

- Although the duration of this effect is not known, it seems prudent to avoid cigarette smoking on the day of collection.

- Direct contamination of the salivette by steroid-containing lotion or oral gels also may result in false-positive results.

Remarks for late-night salivary cortisol

- Finally, stress immediately before the collection also may increase salivary cortisol physiologically
- Ideally, samples should be collected on a quiet evening at home

Remarks for late-night salivary cortisol

- Theoretically, contamination with blood might increase salivary cortisol levels.
- Although Kivlighan et al. reported that minor to moderate blood leakage as a result of vigorous tooth brushing had no effect on salivary cortisol values, the possible effect of gingivitis or oral sores or injury is not known.

Evidence for the 1-mg DST

- At the 1.8mcg/dl cutoff, the sensitivity is high with specificity rates of 80%; specificity increases to > 95% if the diagnostic threshold is raised to 5 mcg/dl.

- Given our objective of using tests with high sensitivity at this stage, we recommend use of the more stringent cutoff of 1.8 mcg/dl

Evidence for the 48-h, 2 mg/d DST

- Certain psychiatric conditions

(depression, anxiety, obsessive compulsive disorder)

- Morbid obesity
- Alcoholism
- Diabetes mellitus

can be characterized by overactivation of the HPA axis but without true Cushing's syndrome, i.e. hypercortisolism is not autonomous

Evidence for the 48-h, 2 mg/d DST

- In these conditions, UFC measurements are less useful as an initial test.
- The optimal test is the LDDST.
- Previous studies using various doses of dexamethasone and differing criteria for suppression suggest that at least 2 wk of abstinence from alcohol are needed to reduce the false-positive rate

Remarks for the 48-h, 2 mg/d DST

- Dexamethasone is given in doses of 0.5mg for 48 h, beginning at 0900 h on d 1, at 6-h intervals, *i.e. at 0900*, 1500, 2100, and 0300 h.
- Serum cortisol is measured at 0900 h, 6 h after the last dose of dexamethasone.
- Yanovski *et al. (9)* proposed a different protocol: administering 48 h of dexamethasone at 6-h intervals but beginning at 1200 h and obtaining serum cortisol at 0800 h, exactly 2 h (rather than 6 h as in the usual protocol) after the last dexamethasone dose.

Retest in mild or cyclic disease

- The recommendation to perform additional testing in patients with discordant results derives from the knowledge that some patients with Cushing's syndrome, usually those with mild or cyclic disease, may have discordant results.

- Also, some patients without Cushing's syndrome may have only a minimally abnormal but discordant result.

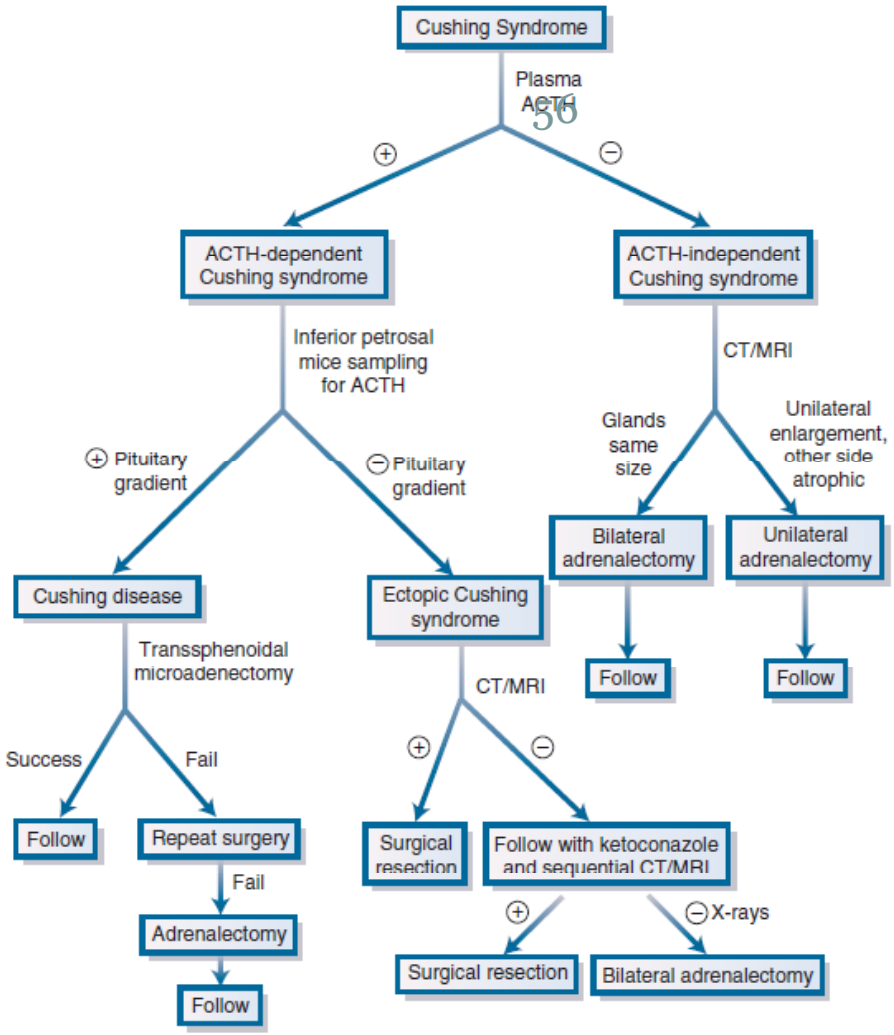

Figure 2-2 Differential diagnosis of Cushing syndrome. This algorithm illustrates the sequential application of the tests of differential diagnosis. There are only four tests: plasma ACTH, petrosal sinus sampling for ACTH, CT, and MRI. This is a good example of the application of the experimental method in medicine (deductive logic). ACTH, adrenocorticotropic hormone; CT, computed tomography; MRI, magnetic resonance imaging.

Subsequent evaluation

For the subsequent evaluation of abnormal initial test results

- Additional use of the dexamethasone- CRH test or the midnight serum cortisol test in specific situations.

Special populations/considerations

1 -Pregnancy:

- Use UFC instead of dexamethasone testing in initial evaluation of pregnant women.

2- Epilepsy:

- Don't use dexamethasone testing in patients receiving antiepileptic drugs known to enhance dexamethasone clearance and recommend measurements of nonsuppressed cortisol in blood, saliva, or urine

Special populations/considerations

- 3 -Renal failure:

use the 1-mg overnight DST rather than UFC for initial testing for Cushing's syndrome in severe renal failure .

- 4 Cyclic Cushing's syndrome:

use of UFC or midnight salivary cortisol rather than DSTs.

- 5 Adrenal incidentaloma:

use 1-mg DST or late-night cortisol test, rather than UFC, in patients suspected of having mild Cushing's syndrome

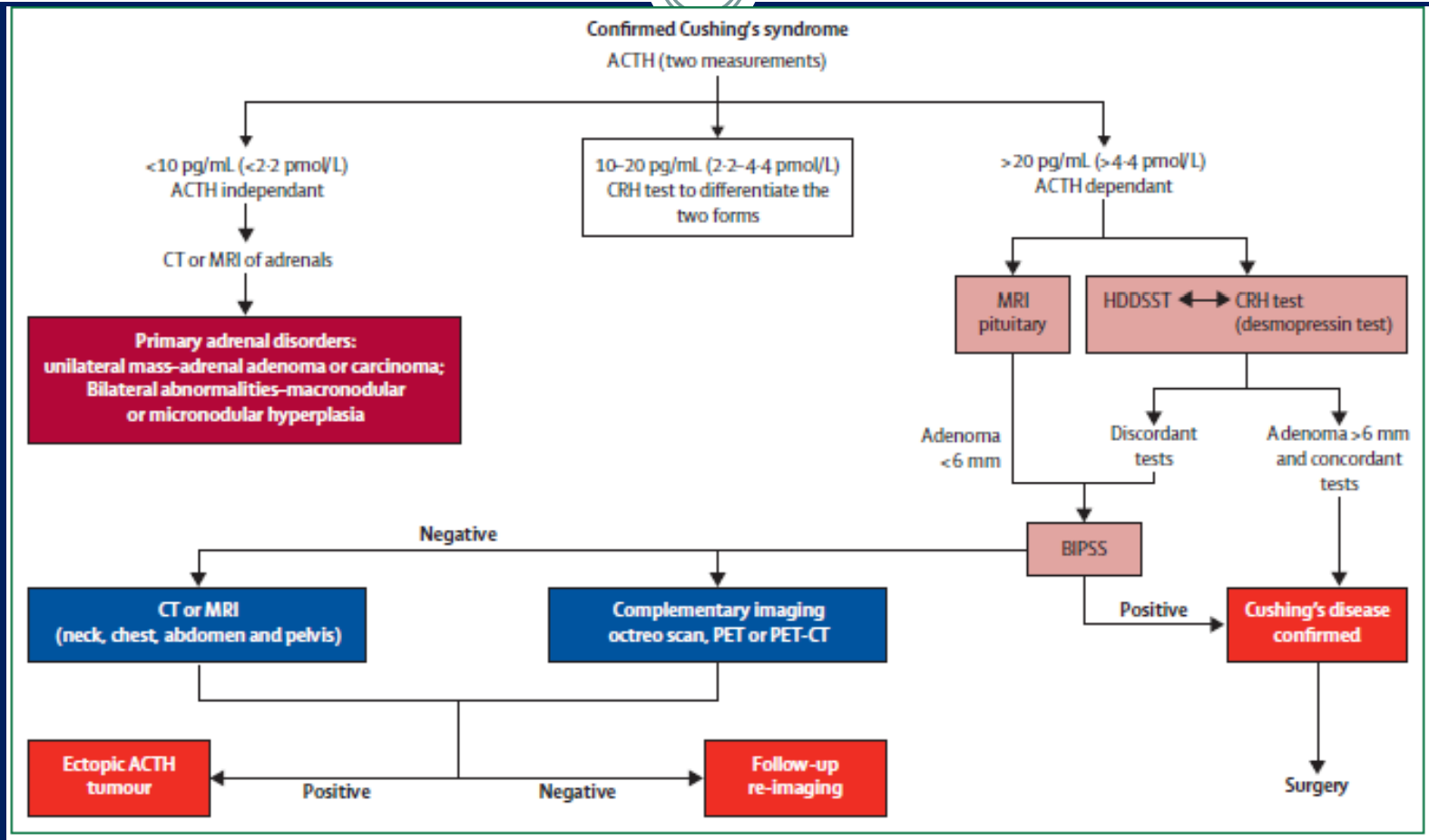

Figure 3: **Clinical decision-making flow chart for the differential diagnosis of confirmed Cushing's syndrome of different causes**
Modified from reference 170 by permission of The Endocrine Society Press. ACTH=adrenocorticotropic hormone. CRH=corticotropin-releasing hormone. HDDSST=high dose dexamethasone suppression test. BIPSS=bilateral inferior petrosal sinus sampling.

Morning Plasma ACTH

- ACTH should be measured with the use of a two-site IRMA.
- Such a test differentiates ACTH-dependent from ACTH-independent causes.

Morning Plasma ACTH

- The samples should be taken in ice cold tubes and immediately separated ahead of storage at –40° C ahead of analysis to prevent inadvertent degradation.

- In Cushing disease, 50% of patients have a 9 AM ACTH within the normal reference range (9 to 52 pg/mL); in the remainder, it is modestly elevated.

Morning Plasma ACTH

- Occasionally, due to episodic secretion, levels may be very low, and thus measurement of at least two values is recommended to avoid misclassification of mild Cushing disease as ACTH-independent.

Morning Plasma ACTH

- ACTH levels in the ectopic ACTH syndrome are high (usually >90 pg/mL); nevertheless, overlap values are seen in Cushing disease in 30% of cases.
- Therefore, this test cannot be used to differentiate the two conditions .

Morning Plasma ACTH

- In patients with adrenal tumors, plasma ACTH is invariably undetectable (<1 pmol/L).
- The presence of plasma ACTH that are low-normal or intermittently detectable, which may occur in MAH, is problematic.

Primary adrenal insufficiency

Who should be tested and how?

- 1 -We recommend diagnostic testing to exclude primary adrenal insufficiency (PAI) in acutely ill patients with otherwise unexplained symptoms or signs suggestive of PAI

- Volume depletion
- Hypotension, hyponatremia, hyperkalemia,
- Fever, abdominal pain, hyperpigmentation or, especially in children, hypoglycemia.

Who should be tested and how?

- 2-We recommend confirmatory testing with the corticotropin stimulation test in patients with clinical symptoms or signs suggesting PAI when the patient's condition and circumstance allow.

- 3- In patients with severe adrenal insufficiency symptoms or adrenal crisis, we recommend immediate therapy with iv hydrocortisone at an appropriate stress dose prior to the availability of the results of diagnostic tests.

Optimal diagnostic tests

- Standard dose (250 mcg for adults and children2 y of age

- IV corticotropin stimulation (30 or 60 min) test to establish the diagnosis of adrenal insufficiency.

Optimal diagnostic tests

- Peak cortisol levels below 500 nmol/L (18 g/dL) (assay dependent) at 30 or 60 minutes indicate adrenal insufficiency.

- We suggest the low-dose (1 mcg) corticotropin test for diagnosis of PAI only when the substance itself is in short supply.

Optimal diagnostic tests

- If a corticotropin stimulation test is not feasible, we suggest using a morning cortisol 140 nmol/L (5 g/dL) in combination with ACTH as a preliminary test suggestive of adrenal insufficiency.

- We recommend measurement of plasma ACTH to establish PAI.

Optimal diagnostic tests

- The sample can be obtained at the same time as the baseline sample in the corticotropin test or paired with the morning cortisol sample.
- In patients with confirmed cortisol deficiency, a plasma ACTH 2-fold the upper limit of the reference range is consistent with PAI.

Optimal diagnostic tests

- We recommend the simultaneous measurement of plasma renin and aldosterone in PAI to determine the presence of mineralocorticoid deficiency.

- We suggest that the etiology of PAI should be determined in all patients with confirmed disease.

Table 2. Major Etiologies of PAI and Associated Features

Etiology	Associated Features
Autoimmune	
Isolated	Not associated with other autoimmune disorders
APS type 1 (APECED)	Chronic cutaneous candidiasis, hypoparathyroidism
APS type 2	Autoimmune thyroid disease, type 1 diabetes
Adrenal—infiltration/injury	
Adrenal hemorrhage	Associated with sepsis, anticoagulants, anti-cardiolipin/lupus anti-coagulant syndrome
Adrenal metastases	Malignancies: lung, breast, colon, melanoma, lymphoma
Infections: adrenalitis	Tuberculosis, HIV/AIDS, CMV, candidiasis, histoplasmosis, syphilis, African trypanosomiasis, paracoccidioidomycosis (eg, in South America)
Infiltration	Hemochromatosis, primary amyloidosis
Bilateral adrenalectomy	Procedure for intractable Cushing's syndrome or bilateral pheochromocytoma
CAH: most forms can cause salt loss	Commonest cause of PAI in children (80%); may be diagnosed in older individuals
21-Hydroxylase deficiency	Commonest type of CAH is 21-hydroxylase deficiency, with associated hyperandrogenism
11β-hydroxylase deficiency	Hyperandrogenism, hypertension (in older children and adults)
3β-hydroxysteroid dehydrogenase II deficiency	Ambiguous genitalia in boys, hyperandrogenism in girls
P450 side-chain cleavage deficiency (CYP11A1 mutations)	XY sex reversal
P450 oxidoreductase deficiency	Skeletal malformations, abnormal genitalia
Congenital lipoid adrenal hyperplasia (StAR mutations)	XY sex reversal
Adrenal hypoplasia congenita	X-linked NROB1, Xp21 deletion (with Duchenne's muscular deficiency), SF-1 mutations (XY sex reversal), IMAGe syndrome
ACTH insensitivity syndromes	Type 1: ACTH receptor, melanocortin 2 receptor gene MC2R Type 2: MRAP Familial glucocorticoid deficiency (MCM4, NNT, TXNRD2) TripleA (Allgrove's) syndrome, achalasia, Addison's disease, alacrima, AAAS gene mutation
Drug-induced	Adrenal enzyme inhibitors: mitotane, ketoconazole, metyrapone, etomidate, aminoglutethimide, drugs that may accelerate cortisol metabolism and induce adrenal insufficiency T_4 also accelerates cortisol metabolism (at least in part through stimulation of 11β-HSD2) CTLA-4 inhibitors may enhance autoimmunity and cause PAI
Other metabolic disorders	Mitochondrial disease (rare) Adrenoleukodystrophy in males Wolman's disease