ENDOCRINE SOCIETY

Cushing's Syndrome
Diagnosis

Consultant:
Endocrine Society Diagnosis of Cushing's Syndrome
Clinical Practice Guideline Writing Committee

Key Points

Diagnosis

⌟ Key Points

- **The most common cause of Cushing's syndrome is iatrogenic from medically prescribed corticosteroids.**
- **Excess cortisol production may be caused by either excess adrenocorticotropic hormone (ACTH) secretion (from a pituitary or other ectopic tumor) or independent adrenal overproduction of cortisol.**
- **The diagnosis can be challenging in mild cases.**
  - Endocrine Society (ES) recommends initial use of one test with high diagnostic accuracy (urine free cortisol [UFC], late night salivary cortisol, 1-mg overnight or 2-mg 48-h dexamethasone suppression test).
  - Testing for Cushing's syndrome in certain high-risk populations has shown an unexpectedly high incidence of unrecognized Cushing's syndrome as compared with the general population. Although there are limited data on the prevalence of the syndrome in these disorders, the diagnosis should be considered.
  - Often patients have a number of features that are caused by cortisol excess but that are also common in the general population such as obesity, depression, diabetes, hypertension, or menstrual irregularity.
  - As a result, there is an overlap in the clinical presentation of individuals with and without the disorder. The distinction between these groups is difficult, and there is no one correct diagnostic strategy.
- **There is a wide spectrum of clinical manifestations at any given level of hypercortisolism. Because Cushing's syndrome tends to progress, accumulation of new features increases the probability that the syndrome is present.**
- **Caregivers are encouraged to consider Cushing's syndrome as a secondary cause of these conditions, particularly if additional features of the disorder are present. If Cushing's syndrome is not considered, the diagnosis is all too often delayed.**
- **Cushing's syndrome tends to progress and severe hypercortisolism is probably associated with a worse outcome, it is likely that early recognition and treatment of mild disease would reduce the risk of residual morbidity.**

➘ Diagnosis

Who Should Be Tested

➤ **ES recommends obtaining a thorough drug history to exclude excessive exogenous glucocorticoid exposure leading to iatrogenic Cushing's syndrome before conducting biochemical testing (1|⊕⊕⊕⊕).**

➤ **ES recommends testing for Cushing's syndrome in the following groups:**

- Patients with unusual features for age (*e.g.,* osteoporosis, hypertension) (Table 1) (1|⊕⊕◯◯)
- Patients with multiple and progressive features, particularly those who are more predictive of Cushing's syndrome (Table 1) (1|⊕⊕◯◯)
- Children with decreasing height percentile and increasing weight (1|⊕◯◯◯)
- Patients with adrenal incidentaloma compatible with adenoma (1|⊕◯◯◯).

➤ **ES recommends against widespread testing for Cushing's syndrome in any other patient group (1|⊕◯◯◯).**

Initial Testing

➤ **For the initial testing for Cushing's syndrome, ES recommends one of the following tests based on its suitability for a given patient (Fig. 1) (1|⊕◯◯◯):**

- UFC (at least two measurements)
- Late-night salivary cortisol (two measurements)
- 1-mg overnight dexamethasone suppression test (DST)
- Longer low-dose DST (2 mg/d for 48 h)

➤ **ES recommends against the use of the following to test for Cushing's syndrome (1|⊕◯◯◯):**

- Random serum cortisol or plasma ACTH levels
- Urinary 17-ketosteroids
- Insulin tolerance test
- Loperamide test
- Tests designed to determine the cause of Cushing's syndrome (*e.g.,* pituitary and adrenal imaging, 8 mg DST).

➤ **In individuals with normal test results in whom the pretest probability is high (patients with clinical features suggestive of Cushing's syndrome and adrenal incidentaloma or suspected cyclic hypercortisolism), ES recommends further evaluation by an endocrinologist to confirm or exclude the diagnosis (1|⊕◯◯◯).**

➤ **In other individuals with normal test results (in whom Cushing's syndrome is very unlikely), ES suggests reevaluation in 6 months if signs or symptoms progress (2|⊕◯◯◯).**

➤ In individuals with at least one abnormal test result (for whom the results could be falsely positive or indicate Cushing's syndrome), ES recommends further evaluation by an endocrinologist to confirm or exclude the diagnosis (1|⊕○○○).

Subsequent Evaluation

➤ For the subsequent evaluation of abnormal initial test results, ES recommends performing another recommended test (Fig. 1, 1|⊕○○○).

➤ ES suggests the additional use of the dexamethasone-suppressed corticotropin-releasing hormone (Dex-CRH) test or the midnight serum cortisol test in specific situations (Fig. 1, 1|⊕○○○).

➤ ES suggests against the use of the desmopressin test, except in research studies, until additional data validate its utility (2|⊕○○○).

➤ ES recommends against any further testing for Cushing's syndrome in individuals with concordantly negative results on two different tests (except in patients suspected of having the very rare case of cyclical disease) (1|⊕○○○).

➤ ES recommends tests to establish the cause of Cushing's syndrome in patients with concordantly positive results from two different tests, provided there is no concern regarding possible non-Cushing's hypercortisolism (Table 2) (1|⊕⊕○○).

➤ ES suggests further evaluation and follow-up for the few patients with concordantly negative results who are suspected of having cyclical disease and also for patients with discordant results, especially if the pretest probability of Cushing's syndrome is high (2|⊕○○○).

Special Populations/Considerations

➤ Pregnancy: ES recommends the use of UFC and against the use of dexamethasone testing in the initial evaluation of pregnant women (1|⊕⊕⊕○).

➤ Epilepsy: ES recommends against the use of dexamethasone testing in patients receiving antiepileptic drugs known to enhance dexamethasone clearance and recommends instead measurements of nonsuppressed cortisol in blood, saliva, or urine (1|⊕⊕⊕○).

➤ Renal failure: ES suggests using the 1-mg overnight DST rather than UFC for initial testing for Cushing's syndrome in patients with severe renal failure (2|⊕○○○).

➤ Cyclic Cushing's syndrome: ES suggests use of UFC or midnight salivary cortisol tests rather than DSTs in patients suspected of having cyclic Cushing's syndrome (2|⊕○○○).

➤ Adrenal incidentaloma: ES suggests use of the 1-mg DST or late-night cortisol test, rather than UFC, in patients suspected of having mild Cushing's syndrome (2|⊕⊕○○).

Table 1. Overlapping Conditions and Clinical Features of Cushing's Syndrome[a]

Symptoms	Signs	Overlapping conditions
Cushing's syndrome features in the general population that are common and/or less discriminatory		
• Depression • Fatigue • Weight gain • Back pain • Changes in appetite • Decreased concentration • Decreased libido • Impaired memory (especially short term) • Insomnia • Irritability • Menstrual abnormalities	• Dorsocervical fat pad ("buffalo hump") • Facial fullness • Obesity • Supraclavicular fullness • Thin skin[b] • Peripheral edema • Acne • Hirsutism or female balding • Poor skin healing	• Hypertension[b] • Incidental adrenal mass • Vertebral osteoporosis[b] • Polycystic ovary syndrome • Type 2 diabetes[b] • Hypokalemia • Kidney stones • Unusual infections
• In children, slow growth	• In children, abnormal genital virilization • In children, short stature • In children, pseudoprecocious puberty or delayed puberty	
Features that best discriminate Cushing's syndrome; most do not have a high sensitivity		
	• Easy bruising • Facial plethora • Proximal myopathy (or proximal muscle weakness) • Striae (especially if reddish purple and >1 cm wide) • In children, weight gain with decreasing growth velocity	

[a] Features are listed in random order.

[b] Cushing's syndrome is more likely if onset of the feature is at a younger age.

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

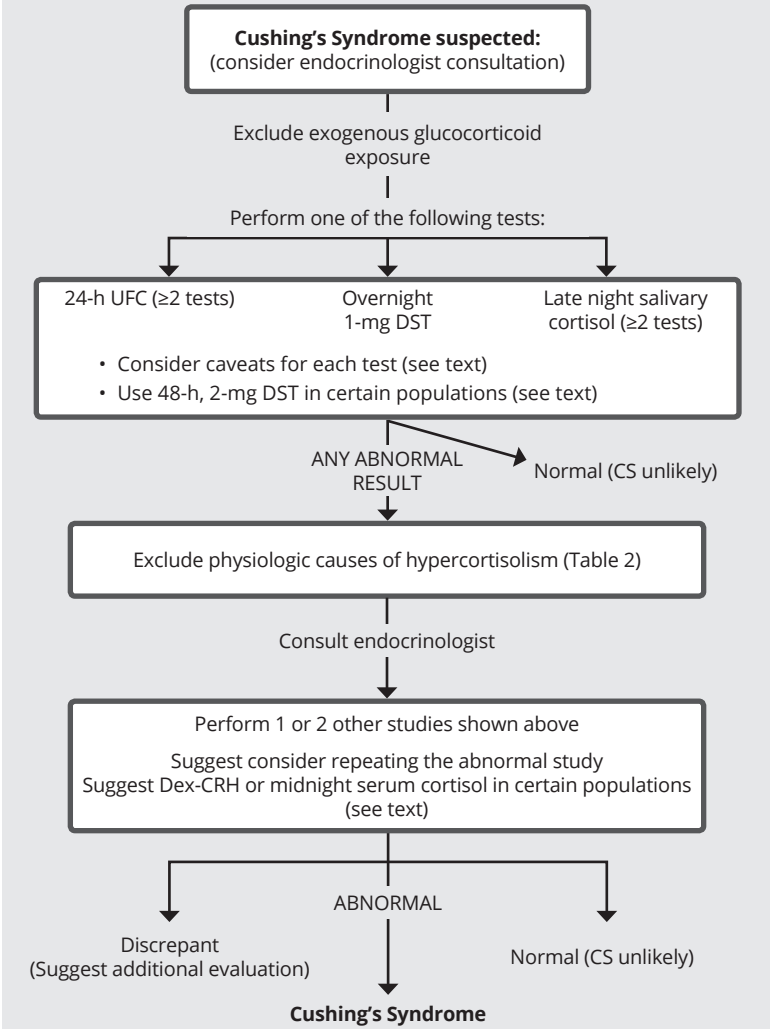
[a] Whereas Cushing's syndrome is unlikely in these conditions, it may rarely be present. If there is a high clinical index of suspicion, the patient should undergo testing, particularly those within the first group.

Table 3. Selected Drugs That May Interfere with the Evaluation of Tests for the Diagnosis of Cushing's Syndrome[a]

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

[a] This should not be considered a complete list of potential drug interactions. Data regarding CYP3A4 obtained from iupui.edu/flockhart/table.htm.

Figure 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).

Grading System				
Strength of Recommendation	1 = strong	2 = conditional		UGPS = ungraded good practice statement
Quality of Evidence	⊕⊕⊕⊕ = high	⊕⊕⊕◯ = moderate	⊕⊕◯◯ = low	⊕◯◯◯ = very low

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Abbreviations

ACTH, adrenocorticotropic hormone; **CBG,** cortisol-binding globulin; **CS**, Cushing's syndrome; **Dex-CRH**; dexamethasone-suppressed corticotropin-releasing hormone; **DST**, dexamethasone suppression test; **HPA**, hypothalamic-pituitary-adrenal; **HPLC**, high-performance liquid chromatography; **11β-HSD2**; 11β-hydroxysteroid dehydrogenase type 2; **LC-MS/MS**, tandem mass spectrometry; **LDDST**, low-dose DST; **17OHCS**, 17-hydroxycorticosteroid; **SMR**, standard mortality ratio; **UFC**, urine free cortisol

Source

Nieman LK, Biller BMK, Findling JW, Newell-Price J, Savage MO, Stewart PM, Montori VM. The Diagnosis of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. May 2008, 93(5):1526–1540.

Disclaimer

This pocket guide attempts to define principles of practice that should produce high-quality patient care. It focuses on the needs of primary care practice, but also is applicable to providers at all levels. This pocket guide should not be considered exclusive of other methods of care reasonably directed at obtaining the same results. The ultimate judgment concerning the propriety of any course of conduct must be made by the clinician after consideration of each individual patient situation. Neither IGC, the medical associations, nor the authors endorse any product or service associated with the distributor of this clinical reference tool.

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