

ONLINE EXCLUSIVE

What's the most practical way to rule out adrenal insufficiency?

Evidence-based answer

A morning serum cortisol level >13 mcg/dL reliably rules out adrenal insufficiency, and the test is easy and safe to perform. Because of low specificity, patients with a level of ≤13 mcg/dL need further evaluation with the cosyntropin stimulation test (CST) (strength of recommendation [SOR]: **A**, meta-analysis of diagnostic cohort studies).

The 250 mcg CST requires intravenous (IV) or intramuscular (IM) administration of

cosyntropin and multiple blood draws; a normal response reliably rules out primary adrenal insufficiency (SOR: **B**, meta-analysis of lower-quality diagnostic cohort studies) and moderately decreases the likelihood of secondary adrenal insufficiency (SOR: **A**, meta-analysis of diagnostic cohort studies). The 1 mcg CST has better diagnostic discrimination, but requires an extra step to dilute the cosyntropin (SOR: **A**, meta-analysis of diagnostic cohort studies).

Evidence summary

The morning serum cortisol level is the most convenient test for adrenal insufficiency because it requires a single blood draw. The 250 mcg CST involves IV or IM administration of cosyntropin and several blood draws. The 1 mcg CST, introduced to improve detection of partial and secondary adrenal insufficiency, requires dilution of the cosyntropin before administration because the smallest available dose is 250 mcg.

The insulin tolerance test is widely considered the gold standard, but requires close observation, is unpleasant for the patient, and carries some risk. Metyrapone and corticotropin-releasing hormone tests are not widely available.¹

Negative CST rules out primary insufficiency

Researchers conducting a meta-analysis of the CST in diagnosing both primary and

secondary adrenal insufficiency searched MEDLINE for English-language studies from 1966 to 2002 and used summary receiver-operating characteristic (ROC) curves to combine the sensitivities and specificities from individual studies.² Four studies of primary adrenal insufficiency showed a negative likelihood ratio of 0.026 for the 250 mcg CST. A negative CST would, therefore, significantly decrease the post-test probability of primary adrenal insufficiency and effectively rule out the condition.

However, primary adrenal insufficiency was already established in the 4 studies, and consecutive testing with an accepted gold standard was not done. Thus, the studies likely overestimate the accuracy of the CST test characteristics.

Using CST results for secondary insufficiency

Twenty studies evaluating the 250 mcg

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FAST TRACK

The morning serum cortisol level is the most convenient test for adrenal insufficiency because it requires a single blood draw.

FAST TRACK

If the morning serum cortisol is <13 mcg/dL, a 1 mcg CST >22 mcg/dL can rule out adrenal insufficiency.

CST for diagnosing secondary adrenal insufficiency were of higher quality. They included patients with and without disease and compared the CST with gold-standard tests, either the insulin tolerance test or metyrapone test. The summary ROC curve indicated a negative likelihood ratio of 0.45, which would decrease only moderately the post-test probability of secondary adrenal insufficiency.

**The 1 mcg CST:
More discriminating than 250 mcg**

Using a ROC curve generated from 22 studies, the authors found the test characteristics of the 250 mcg CST and the 1 mcg CST to be similar. Only 7 of these studies included paired data for the standard- and low-dose CST in the same patients, however. In the 7 studies with paired data, the 1 mcg CST had better diagnostic discrimination, based on a larger area under the ROC, than the 250 mcg CST.

13 mcg/dL is the rule-out threshold for morning serum cortisol

A subsequent meta-analysis, based on a PubMed search of English-language studies from 1966 to 2006, compared the performance of morning serum cortisol, the 1 mcg CST, and the 250 mcg CST for diagnosing secondary adrenal insufficiency. This analysis used patient-level data obtained from the original investigators instead of reported study-level results.³ Data from patients described as normal, healthy control subjects were excluded.

Studies included in the meta-analysis used an accepted gold-standard test, such as the insulin tolerance test or metyrapone test. Studies that were performed in a critical care setting or used older, less reliable cortisol assays were excluded, as were studies for which patient-level data couldn't be obtained. Three new studies were included, and 12 of the previously used studies were excluded.

Instead of using the reported cortisol cutoff levels, the authors defined a negative test as the mean cortisol level (the

“rule-out threshold”) above which the negative likelihood ratio of adrenal insufficiency is <0.15. The rule-out thresholds for morning serum cortisol, 1 mcg CST, and 250 mcg CST were 13, 22, and 30 mcg/dL, respectively.

An optimal testing strategy for secondary insufficiency

The authors proposed an optimal testing strategy for secondary adrenal insufficiency (assuming a low or moderate pretest probability) that starts with a morning serum cortisol measurement:

- A serum cortisol level >13 mcg/dL can effectively rule out adrenal insufficiency.
- If the morning serum cortisol is <13 mcg/dL, a 1 mcg CST >22 mcg/dL can rule out adrenal insufficiency.
- Patients would need an insulin tolerance test or metyrapone test only if the low-dose CST is <22 mcg/dL.

Recommendations

Williams Textbook of Endocrinology states that a basal cortisol level higher than 14.5 mcg/dL invariably indicates an intact hypothalamic-pituitary-adrenal axis. However, to confirm the diagnosis of adrenal insufficiency, all patients, except those with a recent pituitary insult, should undergo a CST. An insulin tolerance test should be done only if the patient has a subnormal response to cosyntropin (to rule out a false-positive CST) or has had a recent pituitary insult.⁴ ■

References

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