

# Review: The cosyntropin-stimulation test has limited value for detecting and excluding adrenal insufficiency

Dorin RI, Qualls CR, Crapo LM. **Diagnosis of adrenal insufficiency.** *Ann Intern Med.* 2003;139:194-204.

## QUESTION

Is the cosyntropin-stimulation test accurate for detecting primary or secondary adrenal insufficiency (AI)?

## DATA SOURCES

Studies were identified by searching MEDLINE (1966 to 2002) using the term adrenal gland hypofunction restricted to diagnosis.

## STUDY SELECTION

Studies were selected if they were published in English, evaluated the diagnosis of primary AI (studies with  $\geq 5$  patients) or secondary AI (studies that stratified all patients with suspected AI by integrated tests of adrenal function [insulin tolerance or metyrapone tests]).

## DATA EXTRACTION

For the 250- $\mu$ g and 1- $\mu$ g doses of the cosyntropin-stimulation test, data were extracted on route of administration (intramuscular or intravenous), time after injection (in min), serum cortisol cutpoint, sensitivity, specificity, and likelihood ratios. Sensitivity and specificity data were combined into summary receiver-operating characteristic (ROC) curves and compared using area under the curves (AUCs).

## MAIN RESULTS

4 studies on primary AI and 29 studies on secondary AI (20 studies using high-dose [250- $\mu$ g] cosyntropin and 9 studies using low-dose [1- $\mu$ g] cosyntropin) were included. Cortisol cutpoints for the diagnosis of primary and secondary AI were 415 nmol/L and 500 to 600 nmol/L, respectively. The high-dose cosyntropin test performed better in detecting primary AI than secondary AI (Table). The 250- $\mu$ g and 1- $\mu$ g cosyntropin tests did not differ for diagnosing secondary AI ( $P > 0.5$  for AUC).

## CONCLUSIONS

The 250- $\mu$ g and 1- $\mu$ g cosyntropin-stimulation tests have similar diagnostic properties. The cosyntropin test may be useful for detecting, but not for excluding, secondary adrenal insufficiency.

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### Summary receiver-operating characteristic analysis of the cosyntropin-stimulation test for primary and secondary adrenal insufficiency (AI)<sup>†</sup>

Primary AI	Number of studies	Sensitivity (95% CI)	+LR (CI)	-LR (CI)	AUC (CI)
High-dose (250 $\mu$ g)	4	97.5% (95 to 100)	19.5 (19 to 20)	0.03 (0 to 0.6)	0.99 (0.98 to 1.0)
<b>Secondary AI</b>					
High-dose (250 $\mu$ g)	20	57% (44 to 71)	11.5 (8.7 to 14.2)	0.45 (0.30 to 0.60)	0.90 (0.87 to 0.94)
Low-dose (1 $\mu$ g)	9	61% (45 to 78)	12.3 (9.0 to 15.5)	0.41 (0.24 to 0.58)	0.91 (0.87 to 0.95)

<sup>†</sup>Cutpoint value for a positive test is set to result in a specificity of 95%. AUC = area under the curve. Other diagnostic terms defined in Glossary.

## COMMENTARY

Systematic reviews may provide highly precise estimates of the properties of diagnostic tests. Such studies may accumulate enough data to link each test result with a magnitude of change in the probability of disease given that particular test result. Further, these reviews can offer evidence of different test performances in different settings or in patients with different spectrums of disease. Unfortunately, the reviews often show that the best available evidence is not definitive, thus the test is of limited value for clinical use. The strongest inference from the review by Dorin and colleagues is that the cosyntropin test performs well in patients with clinically obvious disease (severe and chronic AI), the group in which it is needed the least.

Clinicians considering the diagnosis of primary AI in a patient with nonspecific symptoms may consider measuring plasma cortisol and adrenocorticotropic hormone (ACTH) in a morning sample. If the ACTH assay is not readily available, clinicians may consider the cosyntropin test. Unfortunately, the studies to date have used case-control designs, which systematically overestimate diagnostic test performance

(1). Given that primary AI is rare (in most cases of diagnostic uncertainty, pretest probabilities are very low), patients with a positive cosyntropin test will require additional testing (most positive results are falsely positive) to avoid unnecessary lifelong corticosteroid replacement. Further, a negative test does not exclude mild AI or AI of recent onset. Thus, this test has limited utility for the diagnosis of primary AI.

Similar concerns affect the use of this test to diagnose secondary AI (e.g., in patients admitted to the hospital who recently received corticosteroids). In this setting, clinicians could consider corticosteroid treatment during the stress and later assessment of their endocrine status (with assistance from an expert endocrinologist) when clinically stable.

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### Reference

1. Lijmer JG, Mol BW, Heisterkamp S, et al. Empirical evidence of design-related bias in studies of diagnostic tests. *JAMA.* 1999;282:1061-6.