

# Cushing's Guidelines Clarify When Testing Is Appropriate

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In the absence of exogenous glucocorticoid use, patients with multiple and progressive features that are highly discriminatory for Cushing's syndrome should be tested for the endocrine disorder, according to new clinical practice guidelines developed by a task force of the Endocrine Society.

Testing is also recommended for patients with adrenal incidentaloma compatible with adenoma and children with combined reduced linear growth and increased weight, wrote lead author Dr. Lynnette K. Nieman of the National Institute of Child Health and Human Development and task force colleagues.

Although the signs and symptoms of full-blown Cushing's disease are clinically unmistakable, "the spectrum of clinical presentation is broad, and the diagnosis can be challenging in mild cases," the authors wrote, noting that the guidelines were developed to help facilitate this process. Because the strength of the recommendations varies depending on the quality of evidence supporting them, "careful consideration of the patient's circumstances, values, and preferences is appropriate to determine the best course of action," the authors wrote (*J. Clin. Endocrinol. Metab.* 2008 March 11 [doi:10.1210/jc.2008-0125]).

## Pretest Probability

Before conducting any biochemical testing, physicians should obtain a thorough drug history to rule out iatrogenic Cushing's syndrome associated with excessive exogenous glucocorticoid exposure.

After exclusion of exogenous glucocorticoid use, diagnostic testing is recommended for individuals with multiple features considered discriminatory for the disease, including easy bruising, facial plethora, proximal myopathy, reddish-purple striae, thin skin in the young, and weight gain with decreasing growth velocity in children, the authors wrote.

In addition, because Cushing's syndrome is progressive, patients who demonstrate an accumulation of new features should be tested, as should patients who develop features of the condition, such as osteoporosis and hypertension, which are atypical in the general population for individuals their age. Finally, the presence of an incidentally found adrenal nodule contributes to the pretest probability of Cushing's syndrome. "Such patients usually do not present with overt clinical features of Cushing's syndrome, but biochemical hypercortisolism is present in a large fraction," the authors wrote.

The authors recommend against widespread testing in any other patient group, including obese children, unless their statural growth has slowed.

## Diagnostic Tests

With respect to initial diagnostic testing, the task force recommended any of the following: at least two urinary free cortisol (UFC) measurements, two late-night salivary cortisol measurements, a 1-mg overnight dexamethasone suppression test (DST), or the longer low-dose 2 day/2 mg per day DST.

The guidelines recommend against testing for any of the following because of their low diagnostic accuracy for Cushing's syndrome: random serum cortisol or plasma ACTH levels; urinary 17-ketosteroids; insulin tolerance test; loperamide test; and tests designed to determine the cause of Cushing's syndrome, such as pituitary and adrenal imaging and the 8-mg DST.

Patients with normal test results who have a high pretest probability for Cushing's syndrome based on clinical features, adrenal incidentaloma, or suspect-

ed cyclic hypercortisolism should be referred for further evaluation by an endocrinologist, while those with normal test results and a low pretest probability should be reevaluated in 6 months if symptoms persist. Patients with at least one abnormal test result should also be referred to an endocrinologist for further evaluation to confirm or exclude the diagnosis, the authors wrote.

Although the four recommended diagnostic tests have "acceptable" accuracy when the suggested cutoff points are used, "no test has optimally high specificity, so false positives may occur," the authors noted. To minimize the possibility of a misdiagnosis, the guidelines recommend subsequent evaluation of abnormal initial test results using another one of the high-sensitivity tests. "We suggest the additional use of the dexamethasone-CRH test or the midnight serum cortisol test in specific situations," the authors wrote. They recommended against the use of the desmopressin test, "except in research studies," because its utility has not been validated.

With the exception of patients of having "the very rare case of cyclical disease," further testing is not recommended for patients with negative results on two different tests, the authors noted. For patients with concordantly positive results from two different tests for whom there is no concern regarding possible non-Cushing's hypercortisolism, "we recommend tests to establish the cause of Cushing's syndrome," they wrote. Finally, further evaluation and follow-up is suggested for those few patients with concordantly negative results who are suspected of having cyclical disease, and for those patients with discordant results in whom the pretest probability is high.

## Special Populations

The guidelines also addressed diagnostic testing in special populations, recommending the use of UFC (and against the use of dexamethasone testing) in the initial evaluation of pregnant women, and suggesting the use of the 1-mg overnight dexamethasone suppression test rather than UFC for initial testing in patients with renal failure and in those suspected of having mild Cushing's syndrome. In patients who take antiepileptic drugs that are known to enhance dexamethasone clearance, dexamethasone testing was not recommended. Instead, the guidelines recommended measurements of non-suppressed cortisol in blood, saliva, or urine. When cyclic Cushing's syndrome is suspected, "we suggest the use of UFC or midnight salivary cortisol tests rather than dexamethasone suppression tests," the authors wrote.

There are limited data linking diagnostic strategies to patient outcomes in Cushing's syndrome because "much of the work has focused on developing, validating, and ascertaining diagnostic test performance," the authors wrote. As a result, "the evidence on which many of these recommendations have been made is of low to very low quality," they stated. Additionally, the published data is potentially biased toward more severe cases with higher pretest probability, and thus might not accurately represent the tests' performance in unselected populations in usual clinical practice.

Possible research initiatives that could improve the future care of patients with Cushing's syndrome include the establishment of databases of consecutive patients tested for the syndrome, "allowing for prospective pooling of the diagnostic test information," the authors wrote. Standardization of assays and improved clinical outcome data and targeted clinical trials are also on the authors' wish list. ■

# Consensus Backs Thyroid Screening in the Elderly

BY DOUG BRUNK  
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SALT LAKE CITY — It's hard to know whom among the elderly to screen for thyroid dysfunction because, when it comes to adults without thyroid-disease symptoms, current recommendations from various medical societies differ widely.

The American Thyroid Association recommends screening every 5 years for all women and men older than the age of 35 years. The American College of Physicians' guideline—although officially inactive because it's more than 5 years old—recommends screening only women who are older than 50 and who show incidental symptoms of thyroid disease. And the U.S. Preventive Services Task Force says there is insufficient evidence for or against screening anyone.

Nevertheless, Dr. Naushira Pandya said that the consensus among geriatricians is to screen men and women aged 65 years and older at least once, and thereafter if they develop symptoms of hypothyroidism or hyperthyroidism. The reason, she said, is that so many diseases and drugs common in elderly people can affect the thyroid.

Speaking at the annual symposium of the American Medical Directors Association, Dr. Pandya offered a list of conditions that warrant testing for thyroid dysfunction. These include previous thyroid disease or surgery; the presence of a goiter or nodule; type 1 diabetes; previous postpartum thyroid dysfunction; Down or Turner's syndrome; chronic kidney disease; previous irradiation of the head and neck; radical pharyngeal surgery; history of polycystic ovary syndrome; pituitary surgery or irradiation; and severe head injury.

The list of drugs that affect thyroid function is also lengthy. Lithium, iodine (including that in x-ray contrast media and kelp nutritional supplements), interleukin-2, and interferon- $\alpha$  may cause hypothyroidism, whereas iodine, interleukins, and interferons may cause hyperthyroidism, said Dr. Pandya of the department of internal medicine at Nova Southeastern University College of Osteopathic Medicine, Fort Lauderdale, Fla. In addition, glucocorticoids, io-

dine, propylthiouracil,  $\beta$ -blockers, and amiodarone may impair the conversion of  $T_4$  to  $T_3$ , whereas dopamine, dobutamine, glucocorticoids, phenytoin, bromocriptine, and octreotide may suppress thyroid-stimulating hormone.

Carbamazepine, phenytoin, rifampin, and phenobarbital may increase clearance of  $T_4$ , whereas salsalate, salicylates, nonsteroidal anti-inflammatory drugs, furosemide, and heparin may reduce binding of  $T_4$  to thyroid-binding globulin. Dr.



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DR. PANDYA

Pandya also noted aluminum hydroxide, cholestyramine, ferrous sulfate, sucralose, and cation exchange resins influence the absorption of thyroxine.

Compared with their younger counterparts, older people are more likely to have overt and subclinical hypothyroidism as well as subclinical hyperthyroidism and thyroid nodules, said Dr. Pandya, who is also director of the university's geriatric education center. The prevalence of overt hyperthyroidism and thyroid cancer is believed to be the same in young and old people. However, thyroid cancer in older adults tends to be a more aggressive disease than it is in younger people.

Signs and symptoms of hypothyroidism in older patients mimic certain processes of normal aging, including anorexia, cognitive decline, cold intolerance, constipation, dry skin, fatigue, hearing loss, hoarseness, paresthesia, slowed reflexes, and weakness.

"A high index of suspicion is important," said Dr. Pandya. Symptoms of hyperthyroidism may be absent or subtle, or may be obscured by existing diseases. Cardiac complications such as atrial arrhythmias, heart failure, and angina are the most common indicators of the thyroid problem. A decrease in physical activity with fatigue, weakness, lethargy, agitation, confusion, and dementia are also common. Weight loss with anorexia may be present, and myopathy is predominant. Dr. Pandya said she had no relevant conflicts of interest to disclose. ■