



Complete Summary

GUIDELINE TITLE

The diagnosis of Cushing's syndrome: an Endocrine Society clinical practice guideline.

BIBLIOGRAPHIC SOURCE(S)

The Endocrine Society. The diagnosis of Cushing's syndrome: an Endocrine Society clinical practice guideline. Chevy Chase (MD): The Endocrine Society; 2008. 29 p. [109 references]

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

Cushing's syndrome

GUIDELINE CATEGORY

Diagnosis
Evaluation
Screening

CLINICAL SPECIALTY

Cardiology
Endocrinology
Internal Medicine

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To provide clinical practice guidelines for the diagnosis of Cushing's syndrome

TARGET POPULATION

Patients with clinical features suggestive of Cushing's syndrome, including:

- Patients with unusual features for age (e.g., osteoporosis, hypertension)
- Patients with multiple and progressive features
- Children with decreasing height percentile and increasing weight
- Patients with adrenal incidentaloma compatible with adenoma

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis

1. Thorough drug history of current or recent use of medications
2. Initial testing
 - Urine free cortisol (UFC)
 - Late-night salivary cortisol
 - 1-mg overnight dexamethasone suppression test (DST)
 - Longer low-dose DST
 - Evaluation by an endocrinologist
3. Subsequent evaluation
 - Performance of another recommended test for abnormal initial test results
 - Use of the dexamethasone-corticotropin-releasing hormone (CRH) test or the midnight serum cortisol test
 - Tests to establish the cause of Cushing's syndrome in patients with positive results from two different tests
 - Further evaluation and follow-up for patients with negative results who are suspected of having cyclical disease

Special Populations/Considerations

1. Pregnancy
2. Epilepsy
3. Renal failure
4. Cyclic Cushing's syndrome
5. Adrenal incidentaloma

Note: The guideline developers do not recommend widespread testing for Cushing's syndrome nor the use of the following:

- Random serum cortisol or plasma adrenocorticotrophic hormone (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)

MAJOR OUTCOMES CONSIDERED

- Morbidity
- Standard mortality ratio (SMR)
- Bone mineral density
- Cognitive dysfunction
- Quality of life
- Final stature

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The Task Force used the best available research evidence that members identified and systematic review and meta-analyses of test accuracy to inform the recommendations.

Eligibility Criteria

Cross-sectional and longitudinal studies that enrolled participants with true diagnostic uncertainty were included. Therefore, the diagnosis of Cushing's syndrome (CS) could not be a criterion for enrollment in these studies, so-called phase II and III diagnostic studies. These studies may have included individuals selected because they had physical findings or comorbid conditions suggestive of CS.

Tests of interest were urinary free cortisol (UFC), serum and salivary midnight/bedtime cortisol, 1-mg overnight dexamethasone suppression test (DST) or the 2-d 2 mg DST. Eligible studies had a reference standard for diagnosing CS. Eligible reference standards included a pathological consensus among treating clinicians about a diagnosis of CS). Eligible studies measured the accuracy of test results with results expressed as 1) both sensitivity and specificity or 2) likelihood ratio. Studies were included regardless of their publication status, language, or size.

Study Identification

An expert reference librarian designed and conducted the electronic search strategy with input from study investigators with expertise in conducting systematic reviews. To identify eligible studies, electronic databases (MEDLINE, EMBASE, Web of Science, Scopus, and citation search for key articles) from 1975 through September 2007 were searched. References were also sought from experts.

Reviewers working independently and in duplicate reviewed all abstracts and titles, and upon retrieval of potentially eligible studies, the full text publications for eligibility with adequate chance-adjusted inter-reviewer agreement (kappa statistic = 0.6; 95% confidence interval 0.4-0.7). Disagreements were resolved by consensus or arbitration.

NUMBER OF SOURCE DOCUMENTS

27

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Quality of the Evidence

+000 Denotes very low quality evidence

++00 Denotes low quality evidence

+++0 Denotes moderate quality evidence

++++ Denotes high quality evidence

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Quality Assessment

Reviewers working independently and in duplicate analyzed the eligible articles to assess the reported quality of the methods. The tool for quality assessment of studies of diagnostic accuracy included in systematic reviews (QUADAS) was followed.

Data Extraction

Reviewers working independently and in pairs used a standardized form to extract a full description of study participants, including judgments about the extent of diagnostic uncertainty, the presence of comorbid conditions as eligibility criteria (not as characteristics of the sample), the tests and the procedures followed to conduct them, the cutoff or range definitions of diagnostic tests, whether these cutoffs were derived from previous research or determined by study authors, and the nature and characteristics of the reference standard used. To extract data to estimate diagnostic accuracy measures, we used the cutoffs authors chose to use in the primary studies were used. If more than one cutoff was reported or if the results were reported at the individual patient level, then cutoffs that offered the best test performance were chosen.

Author Contact

Letters were sent to the corresponding authors (or any other author with contact address listed on the main manuscript) of each of the eligible studies by electronic mail (regular mail if an active e-mail could not be obtained). These authors were asked to verify the extracted data and to complete missing data that could not be identified in the published record. In case of no response, the request was repeated 2 weeks later.

Statistical Analysis

Meta-DiSc Software for Meta-analysis for Screening and Diagnostic tests version 1.4 was used. Using random effects meta-analyses, the investigators pooled the sensitivities, specificities, likelihood ratios, and diagnostic odds ratio and estimated the 95% confidence intervals for the outcomes. Because the pooled sensitivity and the pooled specificity are interrelated, analyses were focused on estimating and pooling likelihood ratios and diagnostic odds ratios. The diagnostic odds ratio of a test describes the ratio of the odds of a positive test result in patients with disease compared with patients without disease and can be calculated as the ratio of the likelihood ratios for a positive and a negative test. It has the advantage of being a single indicator of test performance that provides a global meaning of agreement between a test and a reference standard and allows for pooling across studies when the main source of inconsistency is the threshold to consider a test positive (i.e., when there is a common receiver operator characteristic [ROC] curve across all studies).

Summary ROC curves allow readers to visually inspect the consistency of results across studies (answering the question of whether there is a single ROC curve across all these studies) and the accuracy of the test, as judged by the area under the summary ROC curve, in discriminating between patients with and without Cushing's syndrome (CS). In contrast to ROC curves in which individual data points represent different test cutoffs, in summary ROC curves, each point represents a study. The investigators assessed the inconsistency among studies using the I^2 statistic, which represents the proportion of variability across studies that is not due to chance. I^2 values of 25, 50, and 75% indicate low, moderate, and high heterogeneity, respectively.

Subgroup Analyses

A priori hypotheses to explain potential heterogeneity among studies included severity of CS, selection bias (i.e., samples of consecutive patients with high prevalence of CS), type of patients (referred because of clinician's suspicion of CS vs. no CS suspicion), cutoff rationale (driven by outcomes in the same sample, e.g., chosen to maximize specificity, or by the upper limit of the assay), and tests characteristics (sensitivity of the assay, use of liquid chromatography vs. radioimmunoassay [RIA]). These hypotheses were tested using a test for interaction considering $P < 0.05$ as significant, because there were not enough studies to conduct meta-regression.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Participants

The Task Force included a chair, selected by the Clinical Guidelines Subcommittee (CGS) of The Endocrine Society, five additional experts, a methodologist, and a medical writer.

Evidence

Systematic reviews of available evidence were used to formulate the key treatment and prevention recommendations. The authors used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) group criteria to describe both the quality of evidence and the strength of recommendations. The authors used "recommend" for strong recommendations, and "suggest" for weak recommendations.

Consensus Process

Consensus was guided by systematic reviews of evidence and discussions.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Strength of Recommendations

- The number 1 indicates a strong recommendation and is associated with the phrase "The Task Force recommends."
- The number 2 denotes a weak recommendation and is associated with the phrase "The Task Force suggests."

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The guidelines were reviewed and approved sequentially by The Endocrine Society's CGS and Clinical Affairs Core Committee, members responding to a web posting, and The Endocrine Society Council. At each stage the Task Force incorporated needed changes in response to written comments.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Definitions for the quality of the evidence (+000, ++00, +++0, and ++++); the strength of the recommendation (1 or 2); and for the difference between a "recommendation" and a "suggestion" are provided at the end of the "Major Recommendations" field.

Diagnosis

Who Should Be Tested?

The Task Force recommends obtaining a thorough drug history to exclude excessive exogenous glucocorticoid exposure leading to iatrogenic Cushing's syndrome before conducting biochemical testing (1 | ++++).

The Task Force recommends testing for Cushing's syndrome in the following groups:

- Patients with unusual features for age (e.g., osteoporosis, hypertension) (1 | ++00)
- Patients with multiple and progressive features, particularly those who are more predictive of Cushing's syndrome (1 | ++00)
- Children with decreasing height percentile and increasing weight (1 | +000)
- Patients with adrenal incidentaloma compatible with adenoma (1 | +000)

The Task Force recommends against widespread testing for Cushing's syndrome in any other patient group (1 | +000).

Initial Testing

For the initial testing for Cushing's syndrome, the Task Force recommends one of the following tests based on its suitability for a given patient (1 | +000):

- Urine free cortisol (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)

The Task Force recommends against the use of the following to test for Cushing's syndrome

(1 | +000):

- Random serum cortisol or plasma adrenocorticotropic hormone (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), the Task Force recommends further evaluation by an endocrinologist to confirm or exclude the diagnosis (1 | +000).

In other individuals with normal test results (in whom Cushing's syndrome is very unlikely), the Task Force suggests reevaluation in 6 months if signs or symptoms progress (2 | +000).

In individuals with at least one abnormal test result (for whom the results could be falsely positive or indicate Cushing's syndrome), the Task Force recommends further evaluation by an endocrinologist to confirm or exclude the diagnosis (1 | +000).

Subsequent Evaluation

For the subsequent evaluation of abnormal initial test results, the Task Force recommends performing another recommended test (1 | +000).

The Task Force suggests the additional use of the dexamethasone-corticotropin-releasing hormone (CRH) test or the midnight serum cortisol test in specific situations (2 | +000).

The Task Force suggests against the use of the desmopressin test, except in research studies, until additional data validate its utility (2 | +000).

The Task Force 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 | +000).

The Task Force 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 (1 | ++00).

The Task Force 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 | +000).

Special Populations/Considerations

Pregnancy: The Task Force recommends the use of urine free cortisol (UFC) and against the use of dexamethasone testing in the initial evaluation of pregnant women (1 | +++O).

Epilepsy: The Task Force recommends against the use of dexamethasone testing in patients receiving antiepileptic drugs known to enhance dexamethasone clearance and recommend instead measurements of nonsuppressed cortisol in blood, saliva, or urine (1 | +++O).

Renal failure: The Task Force suggests using the 1-mg overnight DST rather than UFC for initial testing for Cushing's syndrome in patients with severe renal failure (2 | +OOO).

Cyclic Cushing's syndrome: The Task Force suggests use of UFC or midnight salivary cortisol tests rather than DSTs in patients suspected of having cyclic Cushing's syndrome (2 | +OOO).

Adrenal incidentaloma: The Task Force 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 | ++OO).

Definitions:

Strength of Recommendations

1 - Indicates a strong recommendation and is associated with the phrase "The Task Force recommends."

2 - Denotes a weak recommendation and is associated with the phrase "The Task Force suggests."

Quality of the Evidence

+OOO Denotes very low quality evidence

++OO Denotes low quality evidence

+++O Denotes moderate quality evidence

++++ Denotes high quality evidence

CLINICAL ALGORITHM(S)

An algorithm for testing patients suspected of having Cushing's syndrome is provided in the original guideline document under Figure 1.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for each recommendation (see "Major Recommendations").

In the original guideline document, each *recommendation* is linked to a description of the *evidence, values* that panelists considered in making the recommendation (when making these explicit was necessary), and *remarks*, a section in which panelists offer technical suggestions for testing conditions, dosing, and monitoring. These technical comments reflect the best available evidence applied to a typical patient. Often this evidence comes from the unsystematic observations of the panelists and should therefore be considered suggestions.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Early detection and diagnosis of Cushing's syndrome may lead to decreased morbidity and mortality and improved quality of life.

POTENTIAL HARMS

- False-positive and false-negative test results may occur
- Potential drug interactions may interfere with the evaluation of tests for the diagnosis of Cushing's syndrome (see Table 3 of the original guideline document for a list of selected drugs)

CONTRAINDICATIONS

CONTRAINDICATIONS

- Dexamethasone clearance may be reduced in patients with *liver and/or renal failure*.
- Because urine free cortisol (UFC) reflects renal filtration, values are significantly lower in patients with *moderate to severe renal impairment*.
- Dexamethasone testing has an increased potential for false-positive results in *pregnancy*.
- UFC appears to be less sensitive than the 1-mg dexamethasone suppression test (DST) or late-night cortisol for the identification of Cushing's syndrome in individuals with *adrenal incidentaloma*.

QUALIFYING STATEMENTS

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- Clinical practice guidelines are developed to be of assistance to physicians by providing guidance and recommendations for particular areas of practice. The guidelines should not be considered inclusive of all proper approaches or methods, or exclusive of others. The guidelines cannot guarantee any specific outcome, nor do they establish a standard of care. The guidelines are not intended to dictate the treatment of a particular patient. Treatment decisions must be made based on the independent judgment of health care providers and each patient's individual circumstances.
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IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Clinical Algorithm
Patient Resources

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

The Endocrine Society. The diagnosis of Cushing's syndrome: an Endocrine Society clinical practice guideline. Chevy Chase (MD): The Endocrine Society; 2008. 29 p. [109 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2008

GUIDELINE DEVELOPER(S)

The Endocrine Society - Disease Specific Society

SOURCE(S) OF FUNDING

The Endocrine Society

GUIDELINE COMMITTEE

Cushing's Syndrome Task Force

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Task Force Members: Lynnette K. Nieman; Beverly M. K. Biller; James W. Findling; John Newell-Price; Martin O. Savage; Paul M. Stewart; Victor M. Montori

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Lynnette K. Nieman, MD (*Chair*)—Financial or Business/Organizational Interests: UpToDate, HRA Pharma, Significant Financial Interest or Leadership Position: none declared

Beverly M. K. Biller, MD—Financial or Business/Organizational Interests: Novartis, consultant, Significant Financial or Leadership Position: none Declared

James W. Findling, MD—Financial or Business/Organizational Interests: Novartis, Corcept, Significant Financial or Leadership Position: none declared

John D. C. Newell-Price, MD, FRCP, PhD—Financial or Business/Organizational Interests: Society for Endocrinology, United Kingdom, Clinical Endocrinology, Trustee to Pituitary Foundation, United Kingdom, Significant Financial Interest or Leadership Position: none Declared

Martin Savage, MD—Financial or Business/Organizational Interests: Society of Endocrinology, RDE, Significant Financial Interest or Leadership Position: Hormone Reproduction, Ipsen

Paul Michael Stewart, MD, FRCP—Financial or Business/Organizational Interests: International Society for Endocrinology, Significant Financial or Leadership Position: none declared

*Victor M. Montori, MD—Financial or Business/Organizational Interests: none declared, Significant Financial or Leadership Position: none declared.

**Evidence-based reviews for this guideline were prepared under contract with The Endocrine Society.*

ENDORSER(S)

European Society of Endocrinology - Medical Specialty Society

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from [The Endocrine Society](#).

Print copies: Available from The Endocrine Society, c/o Bank of America, P.O. Box 630721, Baltimore, MD 21263-0736; Phone: (301) 941-0210; Email: Societyservices@endo-society.org

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Elamin MB, Murad MH, Mullan R, Erickson D, Harris K, Nadeem S, Ennis R, Erwin PG, Montori VM. Accuracy of diagnostic tests for Cushing's syndrome: a systematic review and meta-analyses. *J Clin Endocrinol Metab.* 2008 May;93(5):1553-62. Epub 2008 Mar 11.

Electronic copies: Available to subscribers of the [Journal of Clinical Endocrinology & Metabolism Web site](#).

PATIENT RESOURCES

The following is available:

- Patient guide to the diagnosis of Cushing's syndrome. Chevy Chase (MD): The Hormone Foundation; 2008 May. 2 p.

Electronic copies: Available in Portable Document Format (PDF) from [The Hormone Society Web site](#).

Print copies: Available from The Endocrine Society, c/o Bank of America, P.O. Box 630721, Baltimore, MD 21263-0736; Phone: (301) 941.0210; Email: Societyservices@endo-society.org

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NGC STATUS

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