



Title	The Diagnosis of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline
Journal Reference	Nieman, L. <i>et al.</i> , The Diagnosis of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. <i>The Journal of Clinical Endocrinology & Metabolism</i> , 93(5) 2008, p. 1526–1540
Date of Review:	15/10/18
Summary of Condition (Max 250 words)	<p>Symptoms and signs of disease <u>Features that best discriminate for Cushing's (but low sensitivity):</u> easy bruising, facial plethora, proximal myopathy or muscle weakness, striae (esp. red/purple and >1cm wide), and in children decreasing height velocity and weight gain. <u>Features which are less discriminatory:</u> depression, fatigue, weight gain, decreased libido, impaired memory, insomnia, menstrual abnormalities, obesity, facial fullness, thin skin (more likely to be Cushing's if younger onset), acne, T2DM, hypertension, vertebral osteoporosis, PCOS, hypokalaemia and others.</p> <p>Testing strategy Perform tests to identify cause of Cushing's, as long as there is no concern regarding non-Cushing's hypercortisolism (pregnancy, depression, alcohol dependence, glucocorticoid resistance, morbid obesity or poorly controlled DM).</p> <pre>graph TD A["Cushing's syndrome suspected (consider endocrinologist consultation)"] --> B["Exclude exogenous glucocorticoid exposure"] B --> C["Perform one of the following tests"] C --> D["24-h UFC (≥ 2 tests) Overnight 1-mg DST Late night salivary cortisol (≥ 2 tests)"] D --> E["Consider caveats for each test (see text) Use 48-h, 2-mg DST in certain populations (see text)"] E --> F["ANY ABNORMAL RESULT Normal (CS unlikely)"] F --> G["Exclude physiologic causes of hypercortisolism (Table 2)"] G --> H["Consult endocrinologist"] H --> I["Perform 1 or 2 other studies shown above Suggest consider or repeating the abnormal study Suggest Dex-CRH or midnight serum cortisol in certain populations (see text)"] I --> J["Discrepant (Suggest additional evaluation) ABNORMAL Normal (CS unlikely)"] J --> K["Cushing's syndrome"]</pre> <p>Further notes on initial testing phase</p>

	<p>Use of a longer but lower dose dexamethasone suppression test (DST) (2mg/d for 48 hr) has improved specificity (but lower sensitivity), and can be useful in patients with psychiatric conditions (depression, anxiety or OCD), morbid obesity, alcoholism or DM. Suggest repeat test in 6 month if Cushing's unlikely and signs or symptoms progress.</p> <p><u>Further notes on subsequent investigations:</u> Use dexamethasone-CRH test or midnight serum cortisol if the patient has equivocal or normal urinary free cortisol (UFC) results with high index of suspicion.</p> <p><u>Special considerations</u></p> <ol style="list-style-type: none"> 1. Pregnancy: Use UFC and avoid DST 2. Epilepsy: Use non-suppressed cortisol in blood, saliva or urine and avoid use DST if on anti-epilepsy medication (increases dexamethasone clearance) 3. Renal failure: Use 1mg DST and avoid UFC in severe renal disease 4. Cyclical Cushing's syndrome: use UFC or midnight salivary cortisol and avoid DST 5. Adrenal incidentaloma: Use 1mg DST or late night cortisol test and avoid UFC if mild Cushing's is suspected
<p>Overview of assays used</p>	<p>Guideline does not recommend which methodologies should be employed, but notes certain limitations. Immunoassays (IA) may be affected by cross reactivity with cortisol metabolites and synthetic glucocorticoids. HPLC and LC-MS/MS methods suffer less from cross-reactivity however some drugs (eg carbamazepine and fenofibrate) can positively interfere with chromatographic methods while HPLC and LC-MS/MS have lower upper reference limit (URL) compared to IA.</p> <p>Drugs interference may accelerate dexamethasone metabolism by CYP3A4 (phenobarbital, phenytoin, carbamazepine and others), impair dexamethasone metabolism by inhibiting CYP3A4 (cimetidine, diltiazem, aprepitant and others) or to increase cortisol binding globulin which falsely elevates cortisol concentrations (oestrogens, mitotane).</p> <p>Drugs which interfere with UFC include: carbamazepine, fenofibrate (if HPLC), some synthetic glucocorticoids (IA) and drugs which inhibit 11β-HSD2 (liquorice, carbenoxolone).</p> <p>Suggested cut offs for Cushing's syndrome are:</p> <ul style="list-style-type: none"> • UFC >URL for assay • Serum cortisol >50 nmol/L after 1 mg dexamethasone • Late night salivary cortisol >4 nmol/L
<p>Lab professionals to be made aware</p>	<ul style="list-style-type: none"> ✓ Chemical Pathologist ✓ Clinical Scientist ✓ Biomedical Scientist
<p>Impact on Lab</p>	<p>■ Important</p>
<p>Please detail the impact of this guideline</p>	<p>Diagnosis involves biochemical evidence of raised cortisol, and these test results guide referral decisions.</p> <p>Successful diagnosis can lead to reversal of symptoms and improves patient outcomes. This is notable as in 1952 the 5 year survival rate was just 50% (death often due to vascular or infectious complications).</p>

Impact on Lab

- None:** This guideline has no impact on the provision of laboratory services
- Moderate:** This guideline has information that is of relevance to our pathology service and may require review of our current service provision.
- Important:** This guideline is of direct relevance to our pathology service and will have a direct impact on one or more of the services that we currently offer.

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