Cushing’s Disease
A GUIDE TO IDENTIFYING, DIAGNOSING, AND TREATING CUSHING’S DISEASE
Cushing’s disease is a rare hormonal disorder caused by a pituitary adenoma that secretes excess adrenocorticotropic hormone (ACTH)\(^1-3\)

- Excess ACTH stimulates the adrenal glands to overproduce cortisol leading to the clinical manifestation of Cushing’s disease\(^4\)

Cushing’s disease: rare* and serious

- Prevalence is estimated at 40 cases per million\(^5\)
- Cushing’s disease has an incidence of 1.2 to 2.4 cases/million/year in the United States\(^5\)
- Women are \(3x\) more likely to develop Cushing’s disease, most commonly between ages 30 and 60\(^5,6\)

Cushing’s disease can be confused with more common medical conditions\(^7\)

- Depression
- Obesity
- Polycystic ovary syndrome
- Type 2 diabetes
- Peripheral edema
- Menstrual irregularities

Consider Cushing’s disease when signs and symptoms cannot be explained any other way\(^7\)
The clinical suspicion arises in the presence of central obesity along with the development over time of:

- Reddish-purple striae
- Proximal muscle weakness
- Plethora
- Hirsutism
- Supraclavicular fat pad
- Dorsocervical fat pad
- Unexplained osteoporosis
- Purpura with no obvious trauma
- Skin atrophy
Although biochemical remission or a cure is usually associated with significant clinical improvement, some comorbidities may not completely normalize. Hypertension and diabetes are the main long-term controllable risk factors for cardiovascular events and mortality; repeated follow-up is mandatory.

When Cushing’s disease and its associated comorbidities are successfully treated, the standardized mortality rate improves.
• Evaluating and treating the long-term negative effects of chronic hypercortisolism may be important to reduce morbidity, improve quality of life, and reduce the long-term mortality associated with Cushing’s disease.  

Mortality in patients with Cushing’s disease is 41% higher than that in the general population—even after transsphenoidal surgery (TSS).  

Even transient exposure to excess cortisol is associated with increased mortality.
CUSHING’S DISEASE IS TYPICALLY MISDIAGNOSED

On average it takes 5 to 7 years before Cushing’s disease is diagnosed\(^1\)

Misdiagnosis for several years can occur as a result of\(^4,12,13\):
- Slow-growing tumors
- Slowly progressive symptoms
- Symptoms similar to other common diseases
- Depression or other psychiatric disorders
- Alcoholism
- Poorly controlled diabetes
- Morbid obesity
- Signs and symptoms that vary from patient to patient

Testing is recommended for patients with\(^7\):
- Unusual features for their age such as osteoporosis or hypertension
- Multiple and progressive features, especially those that are more predictive of Cushing’s syndrome such as moon face, dorsocervical fat pad, and central obesity
- Adrenal incidentaloma compatible with adenoma

Early diagnosis and effective treatment are major predictors of **better QoL**\(^11\)

Diagnosing Cushing’s disease is a 2-step approach\(^4\)

**STEP 1:** Excess cortisol synthesis

**STEP 2:** Functional pituitary adenoma

**DIAGNOSE HYPERCORTISOLISM**

**IDENTIFY THE CAUSE OF CORTISOL HYPERSECRETION**
Tests to diagnose Cushing's disease

<table>
<thead>
<tr>
<th>Test</th>
<th>Description</th>
<th>Considerations</th>
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| 24-hour UFC level                              | • Measures free cortisol filtered by the kidney over 24 hours<sup>14</sup>  
• Sensitivity is 45%-71% with 100% specificity<sup>14</sup>  
• Sensitivity may not be optimal for screening<sup>14</sup>  
• Need at least 2 measurements<sup>7</sup>                                                                                                                                                                                                 |                                                                                                                                                                                                            |
| Late-night salivary cortisol                   | • Measures salivary cortisol levels (commonly by an enzyme-linked immunoassay)<sup>14</sup>  
• Sensitivity and specificity are >90%-95%<sup>14</sup>  
• Need at least 2 measurements<sup>7</sup>  
• Test may not be appropriate for shift workers or those with variable bedtimes<sup>7</sup>  
• High sensitivity and ease of testing<sup>7</sup>  
• Cortisol testing is best done at night when cortisol levels are highest<sup>15</sup>                                                                                                                                                                                |                                                                                                                                                                                                            |
| Overnight 1-mg DST                             | • Serum cortisol is measured by RIA  
— Cutoff for serum cortisol is &lt;1.8 μg/dL<sup>7</sup>  
— Sensitivity is &gt;95%<sup>7</sup>  
• Low specificity for diagnosing Cushing’s disease<sup>7</sup>  
• Women taking estrogen may have false-positive result<sup>7</sup>                                                                                                                                                                                                 |                                                                                                                                                                                                            |
| Longer low-dose DST (0.5 mg q6h [2 mg/d] for 48 h) | • Dexamethasone is a synthetic glucocorticoid that normally suppresses ACTH and cortisol<sup>7</sup>  
• Cushing’s syndrome is excluded if the serum concentration of cortisol is &lt;50 nmol/L<sup>7</sup>  
• Absorption and metabolism of dexamethasone may vary from patient to patient, which may influence the result of both the overnight and 48-hour DST<sup>7</sup>                                                                 |                                                                                                                                                                                                            |

ACTH=adrenocorticotropic hormone; DST=dexamethasone suppression test; RIA=radioimmunoassay; UFC=urinary free cortisol.

Magnetic resonance imaging (MRI) may confirm presence of a pituitary tumor and a diagnosis of Cushing’s disease<sup>16</sup>

• MRI reveals a pituitary adenoma in 40%-60% of cases of Cushing’s disease<sup>4</sup>
• Most ACTH adenomas are microadenomas &lt;1 cm in diameter and difficult to detect<sup>4</sup>  
— 85%-87% of patients may present with a microadenoma at the time of diagnosis<sup>17</sup>  
• Even in the absence of a positive MRI, patients with biochemical testing indicative of Cushing’s disease should be referred to an experienced pituitary surgeon for evaluation<sup>4</sup>
PITUITARY SURGERY IS THE RECOMMENDED FIRST-LINE TREATMENT FOR CUSHING’S DISEASE

ANTEROIOR PITUITARY TUMORS AND SURGICAL SUCCESS RATES

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<tr>
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<th>MICROADENOMAS</th>
<th>MACROADENOMAS</th>
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<tr>
<td>SIZE</td>
<td>&lt;10 mm in diameter&lt;sup&gt;9&lt;/sup&gt;</td>
<td>&gt;10 mm in diameter&lt;sup&gt;10&lt;/sup&gt;</td>
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</table>
| FREQUENCY           | Most common<sup>6</sup>  
|                     | Account for 80%-90% of tumors in patients with Cushing’s disease<sup>6</sup>  
|                     | Infrequent<sup>18</sup>  
|                     | Account for ≈6% of tumors in patients with Cushing’s disease<sup>18</sup> |
| SURGICAL SUCCESS RATE | 72.8%<sup>9</sup> | 42.9%<sup>9</sup> |

Surgery may not be curative

Recurrence rates after surgery: 25% up to 5 years and 46% ≥10 years<sup>5,19</sup>

Monitor cortisol levels closely after postsurgical tumor resection

- Within 48 hours postsurgery, most patients in remission* develop a glucocorticoid withdrawal syndrome associated with circulating cortisol levels of <2 μg/dL<sup>4</sup>
- Serum cortisol levels <2 μg/dL after surgery are associated with remission and low recurrence rate of approximately 10% at 10 years<sup>20</sup>

*Remission is generally defined as morning serum cortisol values <5 μg/dL (<138 nmol/L) or UFC <28-56 nmol/d (<10-20 μg/d) within 7 days of selective tumor resection.<sup>3</sup>

Pharmacologic therapy remains an option for patients with persistent disease after surgery, or those who are not candidates for or refuse surgery<sup>5</sup>
PHARMACOTHERAPY CAN BE USED TO MANAGE HIGH CORTISOL LEVELS\(^9\)

Which patients are appropriate for pharmacotherapy?\(^{5,21,22}\)

- Those who are ineligible or unwilling to undergo TSS
- As a second-line treatment in patients for whom TSS did not induce remission (before considering bilateral adrenalectomy or radiotherapy)
- Those waiting for the effects of radiotherapy

THERAPEUTIC TARGETS IN CUSHING'S DISEASE\(^{23}\)

PITUITARY GLAND

- Somatostatin analog: pasireotide\(^1\)
- Dopamine agonist: cabergoline

ADRENAL GLAND

- Steroidogenesis inhibitors: ketoconazole, metyrapone, and osilodrostat\(^1\)
- Adrenolytic drug: mitotane

GLUCOCORTICOID RECEPTOR

- Antagonist: mifepristone
  - Approved in the US for the control of diabetes or glucose intolerance secondary to hypercortisolism in patients who failed surgery or are not surgical candidates\(^9\)

\(^1\)FDA-approved medication for the treatment of Cushing's disease.
Guideline recommendations for ongoing screening and long-term follow-up\textsuperscript{9}

- Monitor cortisol levels regularly to assess patient response to surgical or pharmacologic therapy
- Adjust pharmacologic therapies to address hypo- or hypercortisolism
- Patients who present as clinically suspicious for Cushing’s disease but have normal test results should continue to be followed and retested
- Treat specific comorbidities associated with Cushing’s disease such as psychiatric disorders, diabetes, hypertension, hypokalemia, infections, dyslipidemia, osteoporosis, and poor physical fitness throughout the patient’s life until resolution
- Educate patients and families about the clinical features of remission
When signs of life-threatening complications of Cushing’s disease arise...

The guidelines recommend urgent treatment of hypercortisolism (within 24-72 hours)

Treat immediately if you see signs of any of the following:

- Infection
- Acute psychosis
- Pulmonary thromboembolism
- Cardiovascular complications

Explore additional information about diagnosis and treatment of Cushing’s disease:

- The Pituitary Society
  pituitarysociety.org
- Endocrine Society
  endocrine.org
- NIDDK (National Institute of Diabetes and Digestive and Kidney Diseases)
  niddk.nih.gov
- National Organization for Rare Disorders (NORD)
  rarediseases.org
TREATMENT AND TESTING VIGILANCE CAN IMPROVE THE LIVES OF YOUR PATIENTS WITH CUSHING’S DISEASE

According to the Endocrine Society Clinical Practice Guideline:

• Patients with Cushing’s disease have reduced quality of life compared to patients with other pituitary tumors

• Continue to test for recurrence of Cushing’s disease throughout the patient’s life

Cumulative exposure to excess cortisol is associated with deleterious effects.

By eliminating the associated signs, symptoms, and comorbidities, you may improve quality of life for your patients with Cushing’s disease.

References: