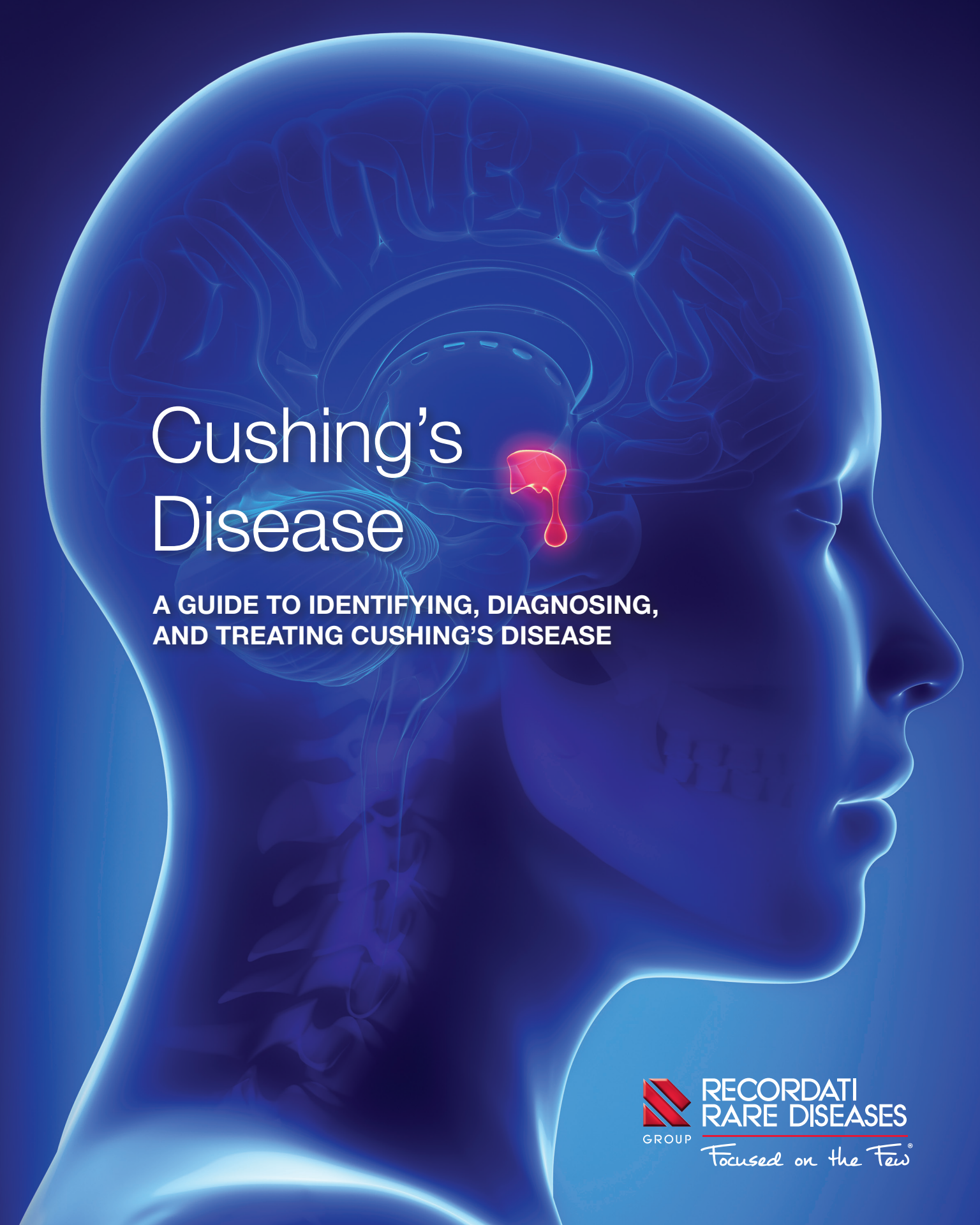
Cushing's
Disease
A GUIDE TO IDENTIFYING, DIAGNOSING,
AND TREATING CUSHING'S DISEASE
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CUSHING'S DISEASE CAUSES ELEVATED CORTISOL[1]

Cushing's disease (CD) is a rare hormonal disorder caused by a pituitary adenoma that secretes excess adrenocorticotropic hormone (ACTH)[1,2]

- Excess ACTH stimulates the adrenal glands to overproduce cortisol, leading to the clinical manifestations of CD[1]

CD is rare* and serious

- Prevalence of nearly ≈40 cases per million[3]
- 1.2 to 2.4 new cases/million/year[3]
- 3× more likely to develop in women, most commonly between ages 30 and 60[3,4]

ALTHOUGH RARE, CD IS THE MOST PREVALENT OF ALL CUSHING'S SYNDROME CASES[5]

60%-70% are caused by an ACTH-secreting pituitary tumor

≈20%-30% are caused by primary adrenocortical tumors

5%-10% are caused by ectopic ACTH-secreting non-pituitary tumors

The signs and symptoms of CD can be confusing[6,7]

- Signs and symptoms vary from patient to patient
- Not all signs and symptoms are obvious, especially early in the progression
- Milder hypercortisolism may not present classically; it may present as a constellation of subtle or inexplicable signs and symptoms

On average, it takes **5 to 7 years** before CD is diagnosed[8]

Consider CD when signs or symptoms cannot be explained with any other diagnosis

*The US Food and Drug Administration defines a rare disease as a condition that affects fewer than 200,000 people.[9]

CLASSIC CD FEATURES MAY NOT ALWAYS PRESENT[6]

Clinical suspicion of CD may arise without a complete picture of classic discriminatory symptoms, especially if other comorbidities are present[10,11]

Signs and Symptoms

- Hair loss[12]
- ⚠ Plethora[11]
- Hirsutism[10,11]
- Dorsocervical fat pad[10,11]
- Supraclavicular fat pad[10,11]
- ⚠ Purpura with no obvious trauma[11]
- Central obesity, unexplained weight gain[10,11]
- ⚠ Reddish-purple striae[10,11]
- Thin skin[10,11]
- ⚠ Proximal muscle weakness[10,11]

⚠ = Classic Discriminatory Symptom.

Clinical Features

- Anxiety or depression[11]
- Obstructive sleep apnea[13]
- Fatigue[6,7]
- Insomnia[6]
- Unexplained osteoporosis[11]
- Insulin resistance[10]
- Carbohydrate intolerance[10]
- Diabetes mellitus type 2[10]
- Hypertension[10,11]
- Dyslipidemia[6,10]
- Irregular menses[11]
- Low libido[11]

CD CAN BE CONFUSED WITH MORE COMMON MEDICAL CONDITIONS[6,7]

Overlapping comorbidities may make diagnosis even more challenging[6,14]

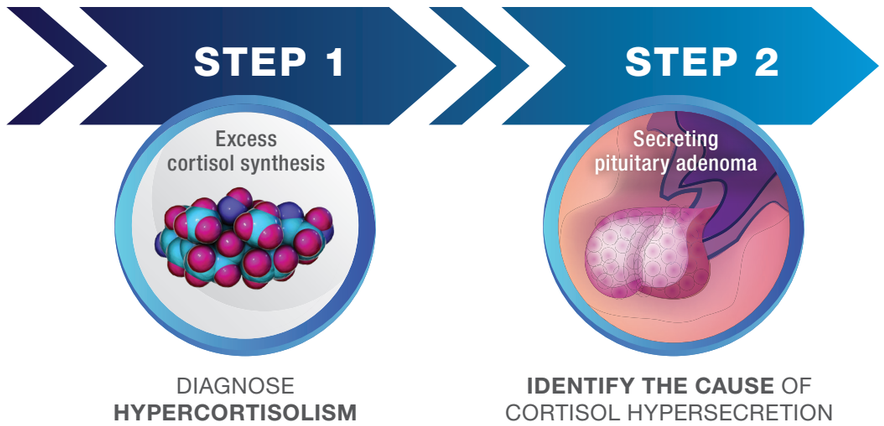
- Depression or other psychiatric disorders[6]
- Morbid obesity[5]
- Menstrual irregularities[6]
- Poorly controlled diabetes[6]
- Peripheral edema[5]
- Polycystic ovary syndrome[10]

A delay in diagnosis can occur as a result of symptoms similar to other diseases[6,11]

When present with any of the discriminatory symptoms of hypercortisolism, consider CD as the cause of other comorbidities, such as[6]:

- Cardiovascular disease
- Glucocorticoid resistance
- Morbid obesity
- Poorly controlled diabetes
- Thromboembolic disease
- Psychiatric deficits
- Cognitive deficits
- Infections

DIAGNOSING CD IS A 2-STEP APPROACH[15]



GUIDELINES RECOMMEND USE OF AT LEAST TWO DIFFERENT TESTS[14]

Tests are complementary and should corroborate each other[14]

- Selections of tests should be individualized to minimize false positives/negatives

TEST	DESCRIPTION	CONSIDERATIONS
24-hour UFC level	• Measures free cortisol filtered by the kidney over 24 hours[16] • Sensitivity is 45%-71% with 100% specificity[16]	• Sensitivity may not be optimal for initial screening[16] • Need at least two measurements[11]
Late-night salivary cortisol	• Measures salivary cortisol levels, commonly by an enzyme-linked immunosorbent assay (ELISA)[16] • Sensitivity and specificity are >90%-95%[16]	• Need at least two measurements[11] • Test may not be appropriate for shift workers or those with variable bedtimes[11] • High sensitivity and ease of testing[11] • Cortisol testing done at night, when cortisol levels are at their nadir, may be useful for assessing changes to its diurnal pattern[17] • May not be as accurate for those with diabetes or obesity and hypertension[11]
Overnight 1-mg DST	• Serum cortisol is measured by RIA — Cutoff for serum cortisol is <1.8 µg/dL[11] — Sensitivity is >95%[12]	• 80% specificity for diagnosing Cushing's disease[11] • Women taking birth control may have false-positive results[11]
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[11] • High sensitivity for diagnosis is maintained if the serum concentration of cortisol cutoff is <1.8 µg/dL[11]	• Absorption and metabolism of dexamethasone may vary from patient to patient, which may influence the result of both the overnight and 48-hour DST[11] • Simultaneous cortisol and dexamethasone tests are recommended to confirm adequate plasma dexamethasone levels[11]

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

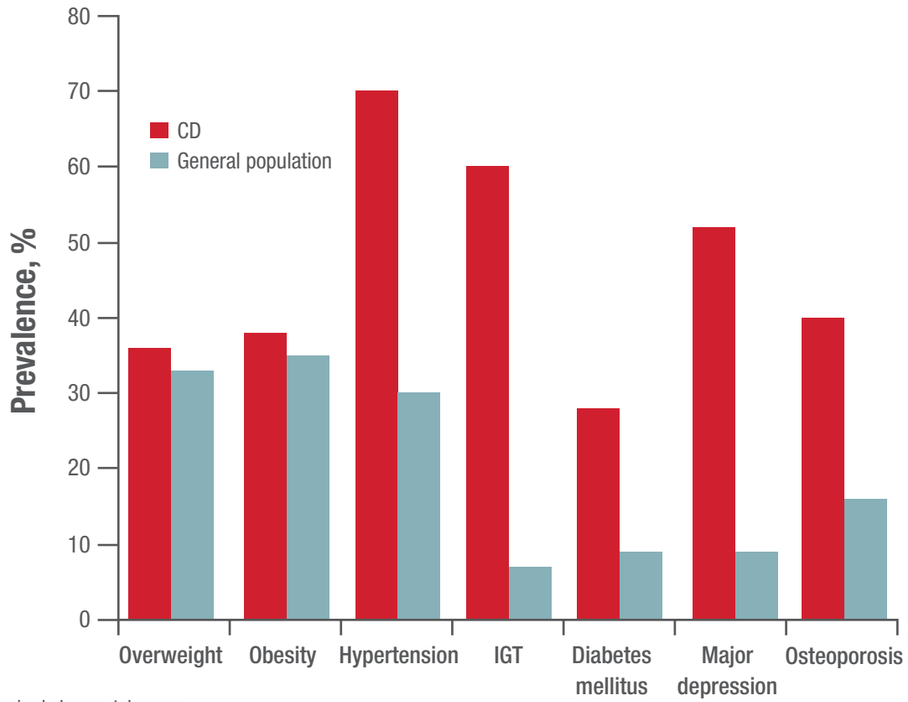
Magnetic resonance imaging (MRI) may confirm presence of a pituitary tumor and a diagnosis of CD[18]

- MRI reveals a pituitary adenoma in 40%-60% of cases of CD[15]
- Most ACTH secreting adenomas are microadenomas <1 cm in diameter and difficult to detect[15]
  — 85%-87% of patients may present with a microadenoma at the time of diagnosis[19]
- Even in the absence of a positive MRI, patients with biochemical testing indicative of CD should be referred to an experienced pituitary surgeon for evaluation[15]

THE DANGERS OF CUMULATIVE EXPOSURE TO EXCESS CORTISOL[3,20]

CD patients experience comorbidities at a higher rate than the general population[1]

PREVALENCE OF COMORBIDITIES ASSOCIATED WITH CD[1]



IGT=impaired glucose tolerance.

- Although biochemical remission or a cure is usually associated with significant clinical improvement, some comorbidities may not completely normalize[20]
- Hypertension and diabetes are the main long-term controllable risk factors for cardiovascular events and mortality; repeated follow-up is mandatory[20]

When CD and its associated comorbidities are successfully treated, the **standardized mortality rate improves**[20]

THE LONGER THE LENGTH OF HYPERCORTISOLISM EXPOSURE, THE GREATER THE MORTALITY RISK[1,21]

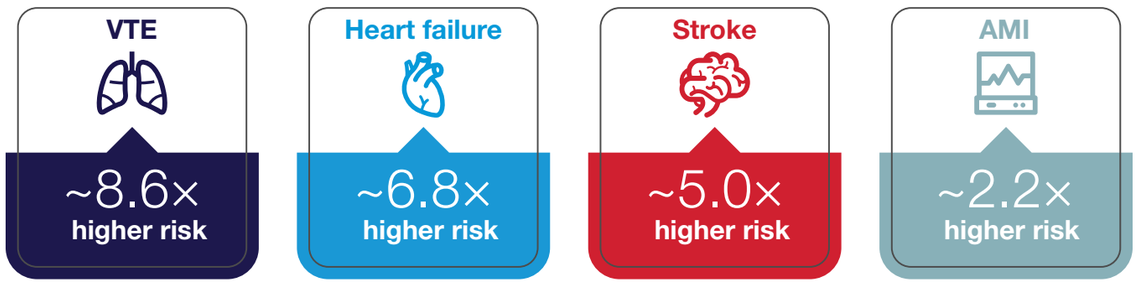
Even transient exposure to excess cortisol is associated with increased mortality[21]

- 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 CD[20]

Uncontrolled chronic hypercortisolism leads to elevated risks of multi-system morbidity and mortality[22,23]

- Patients with chronic, uncontrolled hypercortisolism have a ~3.5-5x higher mortality risk than in the general population[24]

PATIENTS WITH CHRONIC EXPOSURE TO EXCESS CORTISOL ARE AT INCREASED RISK FOR ALL-CAUSE MORBIDITY AND MORTALITY[25]



- The risk of all-cause morbidity and mortality decreases with remission, but is not entirely eliminated[23]

The predicted mortality rate is **nearly 2x higher** for patients with persistent CD vs that for patients in remission[26]

PITUITARY SURGERY IS THE RECOMMENDED FIRST-LINE TREATMENT FOR CD[23]

Pituitary surgery outcomes vary and recurrence is possible[23]

ANTERIOR PITUITARY TUMORS AND SURGICAL SUCCESS RATES

	MICROADENOMAS	MACROADENOMAS
SIZE	• <10 mm in diameter[27]	• >10 mm in diameter[27]
FREQUENCY	• Most common[4] • Account for ≈90% of tumors in patients with CD[27]	• Infrequent[28] • Account for ≈10% of tumors in patients with CD[27]
INITIAL SURGICAL SUCCESS RATE	**89%**[29]	**63%**[29]

Surgery may not be curative for CD

RECURRENCE RATES AFTER SURGERY[3,30]:

~25% up to **5 years** | **~46%** up to **10 years** or more

- Pharmacologic therapy remains an option for patients with persistent disease after surgery or for those who are not candidates for or refuse surgery[3]

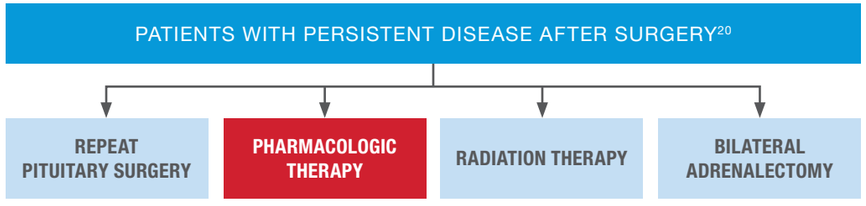
Monitor cortisol levels closely after postsurgical tumor resection

- Within 48 hours postsurgery, most patients in remission* develop a glucocorticoid withdrawal syndrome associated with circulating cortisol levels of <2 µg/dL[15]
- Serum cortisol levels <2 µg/dL after surgery are associated with remission and a low recurrence rate of approximately 10% at 10 years[31]

*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.[22]

PHARMACOTHERAPY CAN BE USED TO MANAGE HIGH CORTISOL LEVELS[20]

Pharmacologic therapy may be an appropriate therapeutic option for patients with persistent disease after surgery[3]



Which patients are appropriate for pharmacotherapy?[3,32]

- Those who are ineligible or unwilling to undergo transsphenoidal surgery (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

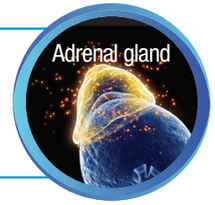
THERAPEUTIC TARGETS IN CD[33]

PITUITARY GLAND

- Somatostatin analog: pasireotide†
- Dopamine agonist: cabergoline

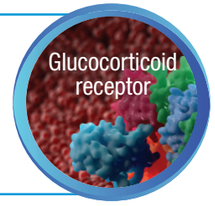
ADRENAL GLAND

- Steroidogenesis inhibitors: ketoconazole, levoketoconazole‡, metyrapone, and osilodrostat†
- 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[20]



Regularly evaluate cortisol levels and other variables according to the prescribing information for individual pharmacologic interventions to confirm therapeutic response[20]

†FDA-approved medication for the treatment of CD.
‡FDA-approved medication for the treatment of CS.

ONGOING TESTING AND MONITORING IS RECOMMENDED AT REGULAR INTERVALS[20]

Monitor to ensure that the patient maintains normalized cortisol levels[3]

TESTS TO MONITOR CD AND FOR ONGOING SCREENING[20,33]

- MONITOR CORTISOL LEVELS REGULARLY TO ASSESS PATIENT RESPONSE TO THERAPY
- ADJUST PHARMACOLOGIC THERAPIES TO ADDRESS HYPER- OR HYPOCORTISOLISM
- TEST FOR RECURRENCE THROUGHOUT LIFE
- MONITOR AND TREAT ANY ADVERSE EVENTS OF THERAPY AND COMORBIDITIES

Guideline recommendations for ongoing screening and long-term follow-up[20]

- Monitor cortisol levels regularly to assess patient response to surgical or pharmacologic therapy
- Adjust pharmacologic therapies to address hypo- or hypercortisolism
- Treat specific comorbidities associated with CD (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

IDENTIFY AND CONTROL CORTISOL LEVELS[20]

Monitor the signs and symptoms of hypercortisolism to help reduce life-threatening complications

When signs of life-threatening complications of CD arise...

The guidelines recommend urgent treatment of hypercortisolism (within 24-72 hours)[20]

TREAT IMMEDIATELY IF YOU SEE SIGNS OF ANY OF THE FOLLOWING:[20]

- Infection
- Acute psychosis
- Pulmonary thromboembolism
- Cardiovascular complications

EXPLORE ADDITIONAL INFORMATION ABOUT DIAGNOSIS AND TREATMENT OF CD:

- pituitarysociety.org
- endocrine.org
- niddk.nih.gov
- rarediseases.org

TREATMENT OF THE CAUSE, AND DISEASE REMISSION, CAN IMPROVE THE LIVES OF YOUR PATIENTS WITH CD[20]

- **Patients with CD have reduced quality of life compared to patients with other pituitary tumors[20]**
- **Continue to test for CD recurrence throughout the patient's life[33]**

Cumulative exposure to excess cortisol is associated with deleterious effects[1]

ACCORDING TO THE ENDOCRINE SOCIETY CLINICAL PRACTICE GUIDELINES, YOU CAN IMPROVE THE LIVES OF YOUR PATIENTS WITH CD BY ACHIEVING REMISSION[20]

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