JAMA | Review

Cushing Syndrome
A Review

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IMPORTANCE Cushing syndrome is defined as a prolonged increase in plasma cortisol levels that is not due to a physiological etiology. Although the most frequent cause of Cushing syndrome is exogenous steroid use, the estimated incidence of Cushing syndrome due to endogenous overproduction of cortisol ranges from 2 to 8 per million people annually. Cushing syndrome is associated with hyperglycemia, protein catabolism, immunosuppression, hypertension, weight gain, neurocognitive changes, and mood disorders.

OBSERVATIONS Cushing syndrome characteristically presents with skin changes such as facial plethora, easy bruising, and purple striae and with metabolic manifestations such as hyperglycemia, hypertension, and excess fat deposition in the face, back of the neck, and visceral organs. Cushing disease, in which corticotropin excess is produced by a benign pituitary tumor, occurs in approximately 60% to 70% of patients with Cushing syndrome due to endogenous cortisol production. Evaluation of patients with possible Cushing syndrome begins with ruling out exogenous steroid use. Screening for elevated cortisol is performed with a 24-hour urinary free cortisol test or late-night salivary cortisol test or by evaluating whether cortisol is suppressed the morning after an evening dexamethasone dose. Plasma corticotropin levels can help distinguish between adrenal causes of hypercortisolism (suppressed corticotropin) and corticotropin-dependent forms of hypercortisolism (midnormal to elevated corticotropin levels). Pituitary magnetic resonance imaging, bilateral inferior petrosal sinus sampling, and adrenal or whole-body imaging can help identify tumor sources of hypercortisolism. Management of Cushing syndrome begins with surgery to remove the source of excess endogenous cortisol production followed by medication that includes adrenal steroidogenesis inhibitors, pituitary-targeted drugs, or glucocorticoid receptor blockers. For patients not responsive to surgery and medication, radiation therapy and bilateral adrenalectomy may be appropriate.

CONCLUSIONS AND RELEVANCE The incidence of Cushing syndrome due to endogenous overproduction of cortisol is 2 to 8 people per million annually. First-line therapy for Cushing syndrome due to endogenous overproduction of cortisol is surgery to remove the causative tumor. Many patients will require additional treatment with medications, radiation, or bilateral adrenalectomy.

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Cushing syndrome results from prolonged elevation in plasma cortisol due to either exogenous steroid use or to excess endogenous cortisol production. The most common cause of Cushing syndrome is exogenous glucocorticoid use from any administration route,[1] including topical or inhaled glucocorticoids.[2] The estimated incidence of Cushing syndrome attributable to endogenous production of cortisol ranges from about 2 to 3 per million people[2] to 8 per million people annually.[3] The most common cause of endogenous Cushing syndrome is Cushing disease, in which a benign pituitary adenoma oversecretes corticotropin.[4] Cushing syndrome from excess endogenous cortisol production may be also caused by a benign or malignant adrenal tumor that secretes cortisol or by a benign or malignant nonpituitary corticotropin-secreting tumor (ectopic Cushing syndrome). Less than 1% of people with Cushing syndrome have a tumor that secretes corticotropin-releasing hormone (CRH).[5]

Elevated cortisol causes hyperglycemia, abnormal protein catabolism, immunosuppression, neurocognitive changes, bone disorders such as osteoporosis, and mood disorders such as depression.[6] Weight gain, hypertension, and hypokalemia are common nonspecific features of Cushing syndrome. Easy bruising, purple striae, and facial plethora are common features that are more specific to Cushing syndrome.[7]

This review summarizes current evidence regarding diagnosis and treatment of Cushing syndrome due to endogenous overproduction of cortisol (Box).[8-10]

Box. Questions Commonly Asked About Cushing Syndrome

What are the most common causes of Cushing syndrome?
The most common cause of Cushing syndrome is use of exogenous glucocorticoids taken orally, inhaled, administered as injections, or used topically in creams and ointments. Cushing disease, caused by a pituitary adenoma that secretes the cortisol precursor corticotropin is the most common cause of Cushing syndrome due to an endogenous cause.

Who should be screened for Cushing syndrome?
All patients with clinical features suspicious for hypercortisolemia and patients with adrenal adenomas should be screened for Cushing syndrome after excluding use of exogenous glucocorticoids.

Which tests should be used to screen for Cushing syndrome?
Three tests are used to screen for elevated cortisol levels: 24-hour urinary free cortisol, late-night salivary cortisol, and dexamethasone suppression testing. For both urinary free cortisol and late-night salivary cortisol, 2 to 3 samples are needed. Because all of these tests can produce false-positive and false-negative results, most patients require more than 1 test to establish a diagnosis of Cushing syndrome. Imaging and bilateral inferior petrosal sinus sampling are used to determine the etiology of endogenous Cushing syndrome. They should not be used for screening.

Methods

We searched MEDLINE, PubMed, and EMBASE for studies of Cushing syndrome epidemiology, diagnosis, treatment, and complications that were published in English between January 2000 and December 2022. The search was updated in March 2023. Articles published between 2017 and 2023 were prioritized for inclusion. We identified 2039 articles published since 2017 and searched reference lists of articles identified for additional relevant publications. We selected 115 articles for inclusion, including 12 clinical trials, 14 systematic reviews and meta-analyses, 6 clinical practice guidelines or consensus statements, 33 general review articles, and 50 articles from registry, cohort, and retrospective studies.

Epidemiology of Cushing Syndrome

The incidence of Cushing syndrome is not well defined. Population-based studies from Sweden, Denmark, and Korea reported that the incidence of endogenous Cushing syndrome was approximately 2 to 3 per million people annually.[2,11-13] The incidence of Cushing syndrome may be higher in the US than in other countries. For example, a health claims database study in the US of patients younger than 65 years reported that the incidence of Cushing disease was approximately 8 per million people annually.[3] The number of people currently living with endogenous Cushing syndrome is unknown. However, Cushing syndrome is believed to be underdiagnosed.[3,13,14] The most common age at diagnosis ranges from 30 through 49 years, but Cushing syndrome can be diagnosed from the ages of 5 to 75 years.[13-16]

Because many symptoms of Cushing syndrome are nonspecific, it is not uncommon for patients to report symptoms for up to 3 years before Cushing syndrome is diagnosed. The time between symptom onset and diagnosis may be even longer for Cushing disease.[17] Pituitary and adrenal adenomas that cause endogenous Cushing syndrome affect women approximately 3 to 4 times more commonly than men, whereas ectopic Cushing syndrome affects men and women similarly.[2,13,14]

Etiology and Pathogenesis of Endogenous Cushing Syndrome

Among patients with Cushing syndrome stemming from excess endogenous production of cortisol, Cushing disease is the underlying cause in approximately 60% to 70% of patients, corticotropin-independent adrenal production of cortisol is the underlying cause in approximately 20% to 30% of patients, and ectopic paraneoplastic neuroendocrine tumors that secrete corticotropin are the underlying cause in about 6% to 10% of patients (**Figure 1**).[5,18] Unilateral adrenal adenoma or carcinoma and bilateral micronodular or macronodular adrenal hyperplasia are the most common causes of Cushing syndrome due to corticotropin-independent adrenal gland production of cortisol.[2,8,19-24]

Cushing Disease

Cushing disease is caused by corticotropin-secreting pituitary adenomas that are typically benign and arise from a monoclonal expansion of corticotroph cells in the anterior pituitary gland.[25] Approximately 90% are microadenomas, defined as less than 10 mm in diameter, and most are less than 6 mm.[26,27] Macroadenomas, 10 mm or more in diameter, account for 10% of corticotroph adenomas.[27,28] Activating somatic gene variants of the ubiquitin-specific protease 8 (*USP8*) gene are identified in about 21% to 60% of adenomas[21] and the *USP48* gene is identified in about 6% to 12%,[29] although their prognostic significance is unclear.[30]

Ectopic Cushing Syndrome

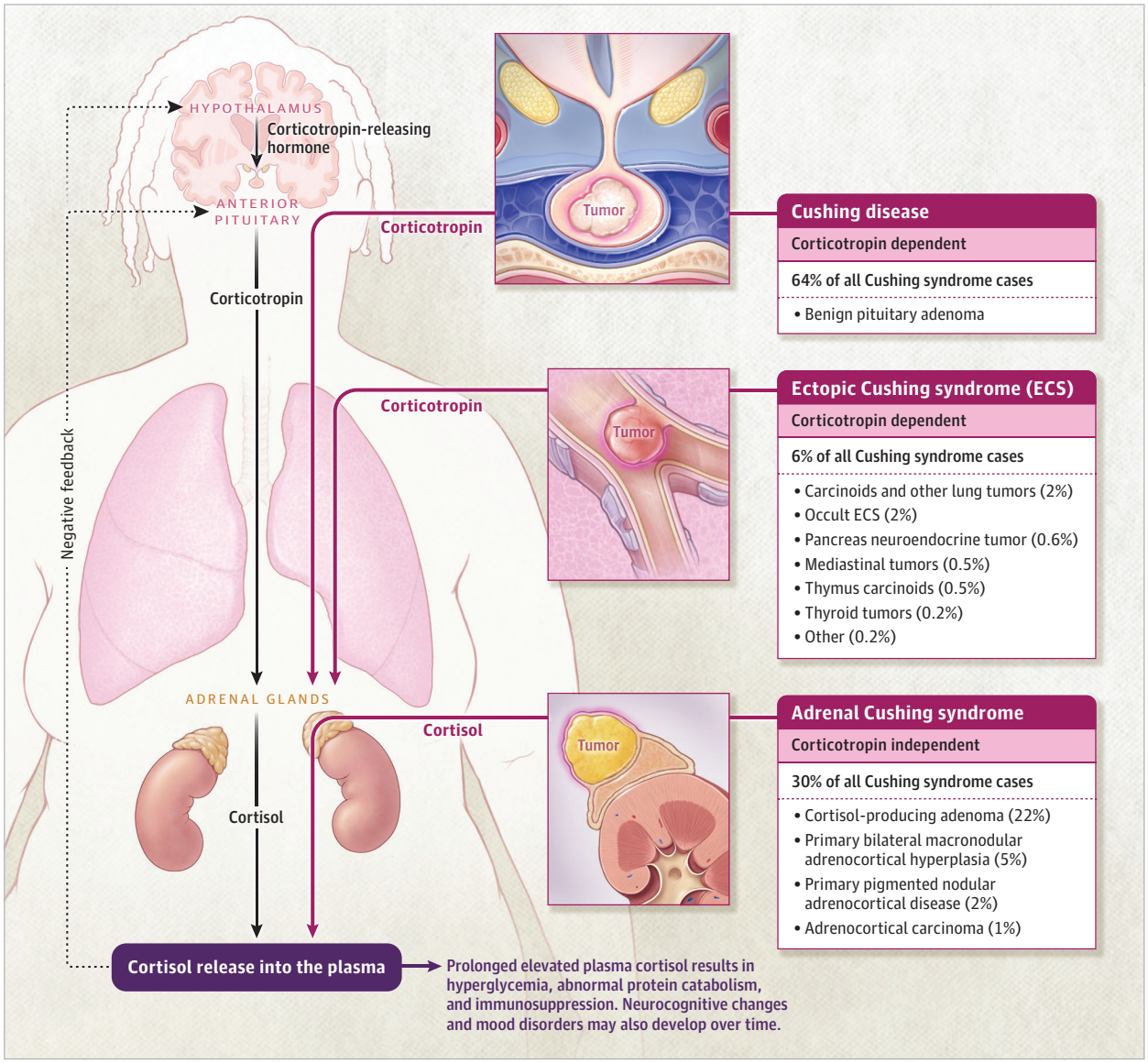
Ectopic Cushing syndrome is predominantly caused by lung, mediastinal, pancreas, and medullary thyroid neuroendocrine tumors that secrete corticotropin. The source of the neuroendocrine tumor is undetected at presentation in approximately 8% to 19% of patients and may remain undetected for years, despite serial imaging over time. Approximately 40% present with metastatic disease.[31] No somatic gene variants have been identified in association with ectopic Cushing syndrome, although some are associated with familial endocrine syndromes, such as multiple endocrine neoplasia type 1.[20]

Adrenal Sources of Cushing Syndrome

Adrenal sources of Cushing syndrome include unilateral cortisol-producing adenomas, which are benign adenomas that originate in the zona fasciculata of the adrenal cortex. Approximately 28% to 50% are associated with somatic gene variants in the catalytic subunit of protein kinase A.[23,32]

Adrenocortical carcinomas are rapidly growing malignant neoplasms with an estimated incidence of 1 to 2 per million people annually.[33] They can occur at any age, but most commonly occur in

Figure 1. Prevalence of Endogenous Cushing Syndrome



Data are based on combined data involving 480 patients in the prospective European Registry on Cushing's Syndrome (ERCUSYN) registry (2000-2010),[5] 1636 patients from a retrospective series in Beijing, China (2008-2017),[18] and 148 patients from the prospective Munich Cushing Registry (2012-2019) (M.R. personal data).

adults aged 40 to 60 years and children younger than 5 years; 55% to 60% occur in females. Tumors are typically 8 to 12 cm in diameter at the time of diagnosis, but approximately 40% do not present with clinically apparent hormone secretion. Distinct molecular cluster of clusters (COC) subtypes are linked to outcomes; COC3, COC2, and COC1 have been associated with poor, intermediate, and better prognosis, respectively.[34]

Primary bilateral macronodular adrenal hyperplasia consists of multiple bilateral adrenal macronodules larger than 10 mm in diameter with hyperplasia and/or internodular atrophy detected on imaging and is responsible for less than 1% of causes of endogenous Cushing syndrome.[35] Primary bilateral macronodular adrenal hyperplasia typically occurs in adults older than 50 years. Inactivating germline variants in the tumor-suppressing armadillo repeat containing 5 (*ARMC5*) gene is present in approximately 21% to 55% of patients with bilateral macronodular adrenal hyperplasia.[24]

Micronodular adrenal hyperplasia occurs in approximately 2% of patients with Cushing syndrome, primarily in children and young adults.[22] Isolated micronodular adrenocortical disease is nonpigmented on histology, which distinguishes it from primary pigmented nodular adrenocortical disease. The latter is associated with familial endocrine syndromes including Carney complex.

Diagnosis of Cushing Syndrome

Cushing syndrome is associated with signs and symptoms that include facial plethora, round face, dorsocervical fat pads, purple striae,

Table 1. Clinical Signs and Symptoms of Cushing Syndrome and Common Laboratory Abnormalities[a]

Frequent and nonspecific for Cushing syndrome, %	Frequent and Cushing syndrome specific, %
Recent weight gain, 70-95	Round face, ≤90
Plethora, 70-90	Osteopenia or osteoporosis and fragility fractures, ≤80
Oligo or amenorrhea, 70-80	Muscle weakness, 60-80
Depression, 50-80	
Hypertension, 60-90	
Hirsutism, 50-75	
Sleep disorders, ≈60	
Dyslipidemia, 40-70	
Decreased libido, 25-90	
Cognitive impairment (exact prevalence unknown)	
Vitamin D deficiency (exact prevalence unknown)	
Less frequent and nonspecific to Cushing syndrome, %	**Less frequent and Cushing syndrome specific, %**
Kidney stones, ≤50	Dorsocervical fat pad, ≈50
Diabetes, ≈30	Purple striae, <50
Atherosclerosis, ≈30	Easy bruising, ≈50
Acne, <50	Thin skin, ≈40
Hair loss, 30	
Laboratory abnormalities[b]	
Increased leukocytes with decreased lymphocytes, eosinophils, monocytes, and basophils	
Elevated glucose and insulin levels	
Hypokalemia	
Increased triglycerides and total cholesterol levels; high-density lipoprotein cholesterol levels are variable	
Elevated liver enzymes	
Changes in activated partial thromboplastin time and plasma concentrations of procoagulant and anticoagulant factors in some patients	
Hypercalciuria, more rarely hypocalcemia, hypophosphatemia, a decrease in phosphate maximum resorption and an increase in alkaline phosphatase activity; elevated magnesium is extremely rare	

[a] Based on data from Braun et al[7] and Pivonello et al.[36]

[b] Varies based on severity of disease and sensitivity to glucocorticoids.

easy bruising, thin skin, fragility fractures, and muscle weakness (**Table 1**),[7] but these signs and symptoms do not occur in all patients with Cushing syndrome.

In patients with possible Cushing syndrome, exogenous glucocorticoid use should be excluded, followed by appropriate diagnostic testing. Abrupt discontinuation of long-term or high-dose exogenous glucocorticoids can induce adrenal insufficiency.

Patients with obesity, metabolic syndrome, polycystic ovary syndrome, uncontrolled diabetes, and eating disorders such as anorexia nervosa may present with mild increases in plasma cortisol (**Table 2**).[37,42] These conditions increase secretion of hypothalamic CRH, which stimulates pituitary corticotropin secretion and adrenal cortisol secretion, resulting in pseudo-Cushing syndrome.[45] Distinguishing pseudo-Cushing syndrome or nonneoplastic hypercortisolism from Cushing syndrome can be difficult. Screening for Cushing syndrome in all patients with diabetes is not recommended and would result in a large number of false-positive results.[2,7] No single symptom is pathognomonic for Cushing syndrome, and elevated plasma cortisol alone is insufficient to diagnose Cushing syndrome.

Testing for Cushing syndrome can be considered in select patients with clinical features strongly associated with Cushing syndrome (Table 1), such as osteoporosis and vertebral fractures, among those younger than 50 years[46,47] and those with incidentally identified asymptomatic adrenal tumors.[48-51]

The diagnosis of Cushing syndrome requires biochemical confirmation of hypercortisolemia, as well as the determination of the underlying cause of excess endogenous cortisol production.[8,45,52] Management of Cushing syndrome is specific to its etiology and an incorrect diagnosis can lead to inappropriate use of medical therapy and/or surgical intervention.

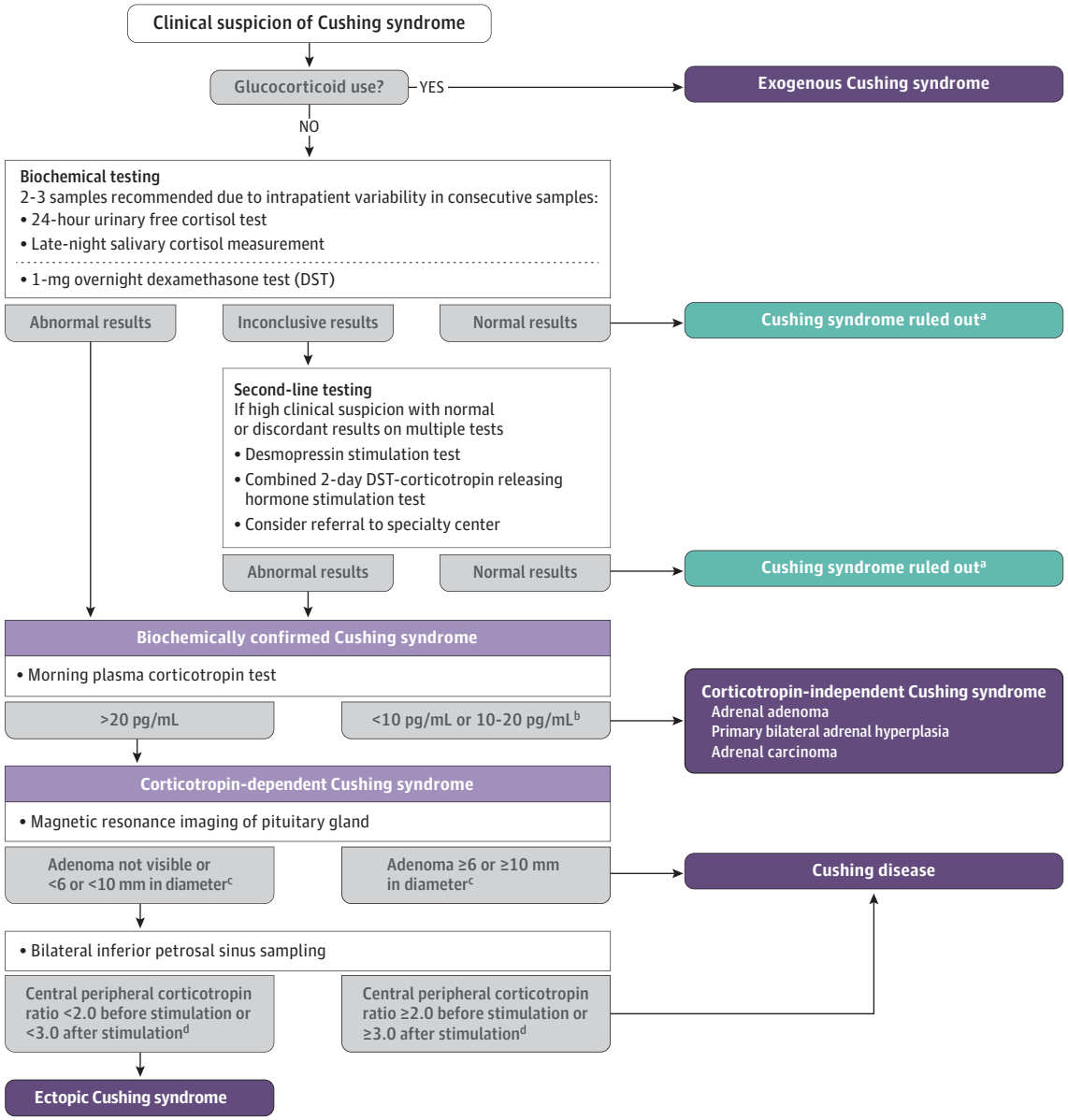
Table 2. Conditions Associated With Physiological, Nonneoplastic Endogenous Hypercortisolism[37-42]

Cause of physiological hypercortisolism	Prevalence
Depression	2.0%-10.4% in general population[39]
Alcohol dependence	4.9% in general population[38]
Glucocorticoid resistance	Unclear, but probably seldom
Obesity	5%-12% in general population, depending on country and age[42]
Diabetes	6.4% in general population[41,43,44]
Pregnancy	0.5%-1.5% of female population, depending on country
Prolonged physical exertion	Unclear
Malnutrition	≤40% in hospitalized patients[37]
Cortisol binding globulin excess	Unclear

Biochemical Evaluation of Endogenous Cushing Syndrome

Diagnostic test selection may be country or center specific based on individual experience, local test performance, and patient-specific considerations. A 24-hour urinary free cortisol test, 1-mg overnight dexamethasone test,[2,8,9,53] and late-night salivary cortisol measurement[2,8,9,53-55] may all be used for initial diagnosis of

Figure 2. Algorithm for the Diagnosis of Cushing Syndrome



After ruling out endogenous sources of excess glucocorticoids, screening for endogenous hypercortisolism should be performed. In cases of abnormal test results. Further testing distinguishes between corticotropin-independent adrenal Cushing syndrome and corticotropin-dependent endogenous Cushing syndrome, then between corticotropin-dependent pituitary Cushing disease and ectopic Cushing syndrome. Recommendations are based on Fleseriu et al[8] and Young et al.[56]

[a] Except cyclic Cushing syndrome.

[b] Plasma corticotropin levels of 10 pg/mL or more and less than 20 pg/mL as well as elevated plasma corticotropin levels but less than 30 pg/mL after stimulation with corticotropin-releasing hormone is suggestive of adrenal Cushing syndrome.[8] To convert corticotropin from pg/mL to pmol/L, multiply by 0.22.

[c] For lesions ranging from 6 mm to 9 mm in diameter, expert consensus differs on use of bilateral inferior petrosal sinus sampling.

[d] Stimulation with desmopressin or corticotropin-releasing hormone.

suspected endogenous Cushing syndrome (**Figure 2**[8,56] and **Table 3**[57-60]). In patients with an adrenal adenoma, dexamethasone suppression is the preferred initial test.[1,8] A random cortisol or corticotropin value is typically only useful in patients with severe symptoms of Cushing syndrome or in patients who have autonomous adrenal production of cortisol with corticotropin suppression.[56,61,62]

Up to 50% of patients have meaningful variability in consecutive samples of late-night salivary cortisol measurement and 24-hour urinary free cortisol test results.[63] To diagnose Cushing syndrome, 2 to 3 measures are recommended for each patient.[8] Two tests may be sufficient to rule out Cushing syndrome in a patient with a low likelihood of having it. For the dexamethasone suppression test, 1 mg of dexamethasone is given between 11 PM and midnight

Table 3. Biochemical Screening Tests for Cushing Syndrome[57-60]

Test	Normal range of cortisol[57,60,a]	Testing principle	How test is performed	Sensitivity and specificity, %	Other considerations
1 mg dexamethasone suppression test	≤1.8 µg/dL	Endogenous overproduction of cortisol is not suppressed by 1 mg of dexamethasone; dexamethasone is a synthetic glucocorticoid that does not have cross-reactivity with the cortisol immunoassay	Oral dexamethasone is administered at 11 PM and plasma cortisol is measured between 8 AM and 9 AM the following day	Sensitivity: 80-95 Specificity: 80-95	Oral estrogen (eg, contraceptive pill) may need to be stopped for several weeks before this test because false-positive rates are increased If the patient does not take the dexamethasone or not absorbed, the result will be a false-positive test result; therefore, dexamethasone can also be measured in some patients
24-h urinary free cortisol	20-80 µg/d (20-45 µg/d in most laboratories)	Increased cortisol excretion over 24 h	Patients collect urine for 24 h starting with a morning collection and 24-h cortisol and creatinine are measured	Sensitivity: 45-71 Specificity: ≤100	Should be performed 2-3 times to improve reliability Impaired test performance in kidney failure 24-h creatinine is needed to properly assess adequacy of 24-h urine collection
Late-night salivary cortisol	A normal salivary cortisol concentration measured at 11 PM is consistent with normal circadian rhythm; cut-off depends on assay used	Elevated night-time cortisol levels	Salivary cortisol is collected through a cotton swab before bedtime, usually between 11 PM and midnight	Sensitivity: 92-100 (varies by assay used) Specificity: 85-100 (varies by assay used)	Should be performed at least 2-3 times to improve reliability of results

SI conversion factor: To convert cortisol from µg/dL to nmol/L, multiply by 27.588.

[a] Normal ranges are assay-dependent and are presented strictly for orientation.

to suppress endogenous corticotropin release and plasma cortisol is measured at 8 AM to 9 AM the following morning. Test accuracy can be improved for the dexamethasone suppression test by measuring both cortisol and dexamethasone levels in the morning between 8 AM and 9 AM.[57]

Clinicians should be familiar with the methods used for testing at their institution and interpret results according to validated diagnostic measures for that method. For example, diagnostic biochemical thresholds established for immunoassays cannot be applied to liquid chromatography mass spectrometry because reference ranges are method and assay dependent. Oral biotin supplementation can interfere with test results when a biotin-avidin separation method is used.[57-60]

For patients with multiple signs and symptoms of Cushing syndrome and who have a high probability of Cushing syndrome, 2 different tests that demonstrated elevated cortisol levels can establish a Cushing syndrome diagnosis.[2,8,9,57] Conversely, 2 test results that fall within the range of normal typically exclude Cushing syndrome.[8-10]

If clinical suspicion of Cushing syndrome is high but test results are normal or yield inconsistent results on multiple tests, second-line tests such as a desmopressin or dexamethasone-CRH test should be performed. Desmopressin, a vasopressin analogue, stimulates corticotropin secretion in patients with Cushing disease and in some patients with neuroendocrine tumors.[56] In contrast, desmopressin does not meaningfully stimulate corticotropin secretion in healthy subjects or in those with nonneoplastic, physiological hypercortisolism.[52] Dexamethasone-CRH testing (patients take 0.5 mg of dexamethasone every 6 hours for 2 days and 2 hours after the last dose of dexamethasone CRH is administered intravenously) can distinguish Cushing disease from nonneoplastic hypercortisolism.[52,55,64] Rarely, patients may have cyclic Cushing syndrome, in which bursts of hypercortisolism are followed by days, weeks, or months of subnormal or normal cortisol secretion, typically manifesting as 2 peaks and 1 trough.[65] The diagnosis can be unclear in patients with mild hypercortisolism or cyclic Cushing syndrome or when tests results are discrepant. In these patients, repeat testing after 3 to 6 months is appropriate,[8,9] and referral to a specialist center is advisable.

Distinguishing Corticotropin-Dependent and Corticotropin-Independent Cushing Syndrome

After establishing the presence of endogenous Cushing syndrome, testing plasma corticotropin between 8 AM and 9 AM can distinguish a corticotropin-dependent from a corticotropin-independent source (Figure 2). Suppressed morning corticotropin levels less than 10 pg/mL (to convert corticotropin from pg/mL to pmol/L, multiply by 0.22) on at least 2 tests performed on different days indicates corticotropin-independent adrenal Cushing syndrome, such as adrenal adenomas, primary bilateral adrenal hyperplasia, or adrenal cancer. Normal or elevated morning plasma corticotropin levels of 10 pg/mL or higher indicates corticotropin-dependent Cushing disease or ectopic Cushing syndrome. Extremely elevated levels, such as those exceeding 250 pg/mL, are more common in patients with ectopic Cushing syndrome than in Cushing disease, but there is substantial overlap in corticotropin values between the 2 conditions. Morning plasma corticotropin levels in the range of 10 pg/mL and 20 pg/mL are indeterminate (inconclusive)[8,66] and

may indicate that adrenal steroid production is inadequate to fully suppress corticotropin.

Differentiating Between Cushing Disease and Ectopic Cushing Syndrome

If corticotropin-dependent Cushing syndrome is confirmed and magnetic resonance imaging (MRI) shows pituitary adenoma, guidelines suggest bilateral inferior petrosal sinus sampling if the pituitary adenoma is less than 6 to 10 mm in diameter.[2,8] However, due to cost, invasiveness, and availability, some centers restrict this test to patients with inconclusive biochemical tests and/or imaging studies.[67] Although bilateral inferior petrosal sinus sampling is the best practice for localizing the corticotropin excess source to the pituitary, it should not be used for patients without previously confirmed corticotropin-dependent Cushing syndrome.[2,8]

As an alternative to bilateral inferior petrosal sinus sampling, stimulation with CRH and/or desmopressin, and rarely a high-dose dexamethasone test, may be used to differentiate Cushing disease from ectopic Cushing syndrome.[2,8,9,53-55,57,68] In this setting, tests are based on the principle that corticotropin-secreting pituitary adenomas respond to stimulation with CRH or desmopressin by increasing corticotropin production[69,70] and respond to dexamethasone by reducing corticotropin production.[69] In contrast, corticotropin levels in patients with ectopic Cushing syndrome remain unchanged with stimulation by CRH or desmopressin[69] or in response to dexamethasone.

Diagnostic Imaging

Pituitary MRI

Corticotropin-secreting corticotroph adenomas are typically small lesions less than 6 mm in diameter that can be visualized on high-resolution 1.5 T or 3.0 T gadolinium-enhanced MRI. Among 159 patients with confirmed Cushing disease, 46% had microadenomas on pituitary MRI, 9% had macroadenomas, 23% had possible lesions detected, and 23% had a normal MRI finding.[28] During follow-up and with more advanced imaging modalities, more than 70% of patients had a definite or probable abnormal MRI finding. Artifacts and nonfunctioning microadenomas should also be considered if adenomas smaller than 6 mm are seen on MRI.

Diagnosing Ectopic Cushing Syndrome

More than 70% of patients with established ectopic Cushing syndrome have a neuroendocrine tumor above the diaphragm, and 20% to 40% have a neuroendocrine tumor in the chest.[56] Thus, initial imaging should consist of computed tomographic (CT) evaluation of the neck, thoracic cavity, and abdomen.[22] Lung neuroendocrine tumors are typically peripheral, small round lesions proximal to the bronchi, and bronchial neuroendocrine tumors account for most occult lesions not visible on imaging.[56] In patients with occult tumors, repeat pituitary high-resolution gadolinium-enhanced MRI is needed to identify a possible pituitary source of corticotropin hypersecretion.[71]

Cervical and thyroid ultrasonography can be used to identify primary or metastatic medullary thyroid carcinoma. Functional imaging with a gallium 68 dotatate positron emission tomographic (PET) scan, which has higher sensitivity for detecting tumors than do CT scans, can detect lesions in 60% to 75% of all patients with ectopic Cushing syndrome, but it is not widely available.[72] Fluourodopa F 18 PET scans can be used for corticotropin-producing paragangliomas and pheochromocytomas, and fluorodeoxyglucose F 18 PET scans are useful for identifying rapidly proliferating neuroendocrine tumors. Repeat imaging after 6 to 12 months may be needed if initial test results are negative for localizing tumors.[56]

Adrenal Imaging

Unilateral adrenal adenomas are usually small, with native fat equivalent density values less than 10 Hounsfield units (HU) and rapid contrast washout on contrast-enhanced CT scans. Adrenocortical carcinoma has an inhomogeneous tissue pattern with necrosis, calcifications, and more than 10 HU on unenhanced CT scans and with delayed contrast washout. Primary bilateral macronodular adrenal hyperplasia has pathognomonic nodules with an appearance like clusters of grapes in both adrenal glands on adrenal CT imaging and hyperplastic or atrophic adrenal cortex between nodules.[73] Approximately 30% of patients with micronodular adrenal hyperplasia have adrenal glands that appear normal on a CT scan. Alternatively, the CT may show slightly hyperplastic adrenal glands with micronodules, usually smaller than 6 mm in diameter.

Management

For patients with endogenous Cushing syndrome, the primary aim of therapy is complete resection of the underlying tumor.

Monitoring for biochemical remission with 24-hour urinary free cortisol, dexamethasone suppression, and late-night salivary cortisol testing is important because clinical manifestations may lag behind biochemical evidence.

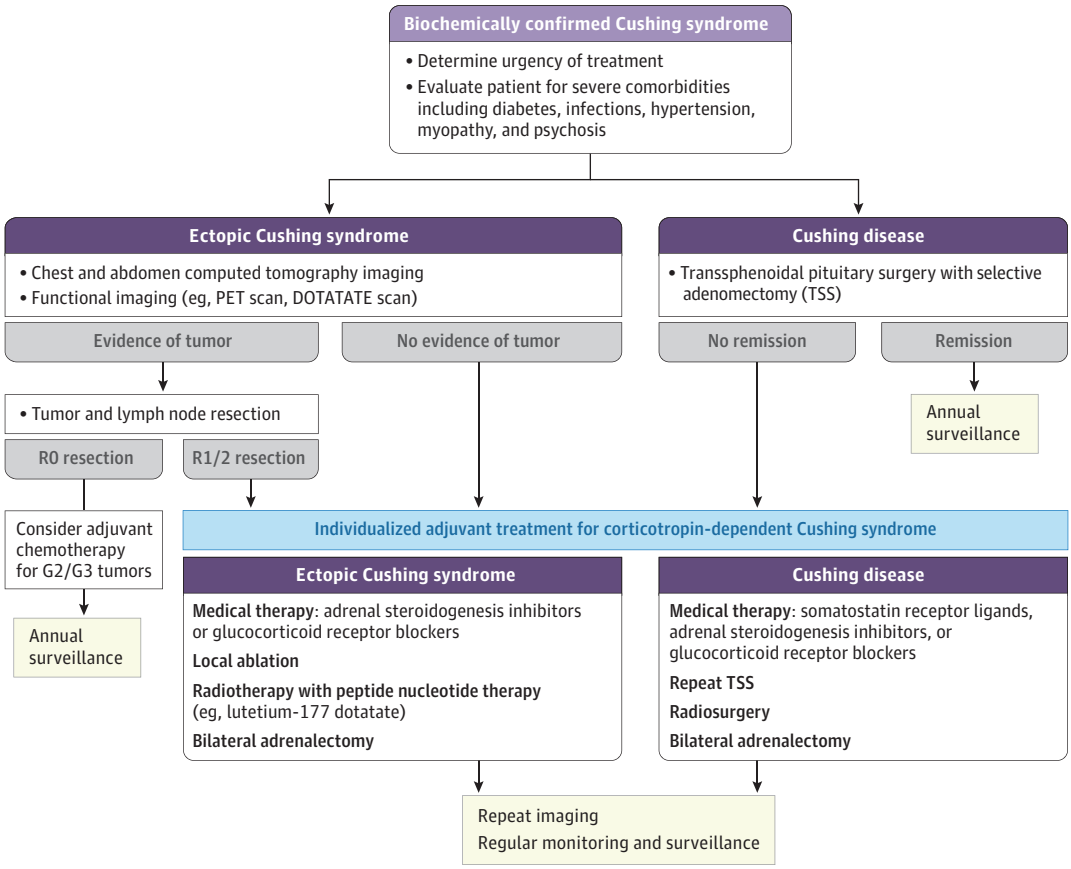
In case of recurrence or if primary surgery is not feasible, medical therapy, radiation therapy, and adrenalectomy are potential therapeutic options (**Figure 3**). An individualized approach, taking patient values and preferences into consideration, is recommended.[8,74]

Surgery

Transsphenoidal pituitary surgery with selective adenomectomy is the primary therapy for Cushing disease (Figure 3).[8,74,75] Median biochemical remission rates after transsphenoidal surgery are approximately 80% in specialized centers.[76,77] Postoperative complication rates such as anterior hypopituitarism, diabetes insipidus, and cerebrospinal fluid leak occur in less than 20% of patients. Central adrenal insufficiency develops postoperatively in all patients who are in remission and frequently persists for more than 1 year, requiring supraphysiological glucocorticoid doses followed by slow tapering to avoid glucocorticoid withdrawal syndrome[78] and secondary adrenal insufficiency.[78,79] Life-long clinical and biochemical follow-up is recommended for early detection of adenoma recurrence. Repeat surgery can be considered for select cases, if the adenoma is visible and remission could be achieved. Bilateral adrenalectomy is infrequently performed because it requires permanent glucocorticoid and mineralocorticoid replacement and because adrenalectomy may stimulate pituitary adenoma growth because of loss of corticotropin-cortisol feedback. This phenomenon is known as *corticotroph tumor progression* or *Nelson syndrome*.[8,74]

For patients with ectopic Cushing syndrome, tumor resection including removal of locoregional lymph nodes is the treatment of

Figure 3. Algorithm for Treatment of Corticotropin-Dependent Cushing Syndrome



Recommendations are based on Fleseriu et al[8] and Young et al.[56] PET indicates positron emission tomography.

choice but is feasible only when the tumor is identified on imaging and can be safely resected (Figure 3). Surgical success rates for total tumor resection and biochemical remission of Cushing syndrome vary from a low of 30% to a high of nearly 60%, depending on the type of neuroendocrine tumor, severity of hypercortisolism, presence of metastases, and other factors.[56,80] Bilateral adrenalectomy is often recommended for patients with severe ectopic Cushing syndrome because it has an immediate effect on relieving hypercortisolism and can stabilize the patient, facilitating later oncological treatments. But risks of intraoperative complications are higher among these patients.[56]

Laparoscopic adrenalectomy is the established treatment for Cushing syndrome induced by unilateral benign cortisol-producing adenomas and is associated with low morbidity (3%-7%) and mortality (≈ 0.5%) rates[81,82] but requires perioperative and postoperative glucocorticoid replacement therapy because of corticotropin suppression and central adrenal insufficiency.[83] Open surgery with locoregional lymphadenectomy is the standard approach for patients who may have adrenocortical carcinoma.[84] In primary bilateral macronodular adrenal hyperplasia, laparoscopic bilateral adrenalectomy is standard care. Unilateral resection of the adrenal gland with the larger tumor has been advocated in asymmetric primary bilateral macronodular adrenal hyperplasia[85,86] and for some patients with primary pigmented nodular adrenal disease[87] to avoid the lifelong requirement for glucocorticoid replacement and the risk of adrenal crisis, which manifests as hypotension, circulatory shock, and premature death.

Medical Therapy

When surgical therapies have failed or are not feasible,[4,8,74] medical therapy has been increasingly used for all types of endogenous Cushing syndrome as symptomatic treatment to control hypercortisolism. Inhibitors of adrenal steroidogenesis are an established treatment for hypercortisolism in patients with all forms of endogenous Cushing syndrome,[8,74] especially among patients who are not candidates for surgery or who have persistence or recurrence of the underlying tumor.[4] Osilodrostat is approved in the US for Cushing disease and levoketoconazole is approved in the US for Cushing syndrome. Ketoconazole, metyrapone, and osilodrostat are approved in Europe and other regions for Cushing syndrome. Mitotane is approved for adrenal cancer.[4,8] Ketoconazole, metyrapone, and etomidate have been used off-label in the US for all forms of Cushing syndrome.[4,8,74,88-92]

Due to their efficacy and rapid onset of action, these agents can be used for both long-term and acute treatment of life-threatening hypercortisolism such as in patients with immunosuppression and sepsis (eTable in the Supplement).[4,8,74] Within this steroidogenesis inhibitor class of drugs, osilodrostat is the most

potent in decreasing cortisol, but symptoms consistent with possible adrenal insufficiency may occur in almost half of the patients.[93] Doses should be increased slowly and close observation is needed.[4,8,93,94] Mitotane is the preferred drug for patients with adrenocortical carcinoma.[74]

Therapies specific for Cushing disease, including the somatostatin receptor ligand pasireotide[95,96] and cabergoline, a dopamine D_2 receptor agonist, which is not approved by the US Food and Drug Administration for this indication,[97,98] have lower efficacy than steroidogenesis inhibitors in decreasing cortisol but could be useful for patients with macroadenomas.[99] Hyperglycemia with pasireotide occurs in as many as 80% of patients,[96] so increased awareness and prompt treatment is needed.[8]

The glucocorticoid receptor antagonist mifepristone was approved in the US for treatment of hyperglycemia in adult patients with endogenous Cushing syndrome who have diabetes or glucose intolerance.[100] Cortisol levels cannot be used to monitor effectiveness of mifepristone because the drug acts at the glucocorticoid receptor and does not affect cortisol secretion. The drug is titrated based on clinical and biochemical consequences of cortisol excess, including hyperglycemia and body weight. Overtreatment can lead to adrenal insufficiency and cortisol cannot be used for diagnosis of adrenal insufficiency in these cases. Treatment of adrenal insufficiency requires higher doses of glucocorticoids (2-4 mg dexamethasone).

Many patients, especially those with ectopic Cushing syndrome and adrenocortical carcinoma, require combination medical therapy, such as with multiple adrenal steroidogenesis inhibitors simultaneously.[33,56]

Neuroendocrine tumors may be treated with chemotherapy and/or the somatostatin receptor ligands octreotide or lanreotide in conjunction with adrenal steroidogenesis inhibitors.[56] For adrenocortical carcinomas, mitotane can be given with a chemotherapy regimen of etoposide, doxorubicin, and cisplatin.[84]

Radiation Therapy

Radiation can be used as adjuvant treatment for patients with endogenous Cushing syndrome who do not achieve remission with surgery.[8,101] In Cushing disease, stereotactic radiation to the remaining pituitary tumor is highly effective in an estimated 92% of patients.[8,101] Treatment with stereotactic radiation attains biochemical remission and reduces cortisol levels more quickly than conventional radiation, but biochemical remission at 5 years is only 50% to 65%.[8,101] Approximately 20% develop new-onset hypopituitarism.[8,101]

For patients with metastatic neuroendocrine tumors and ectopic Cushing syndrome, radiation therapy is most frequently administered as systemic radiotherapy with peptide nucleotide therapy (eg, lutetium-177 dotatate).[102] Although radiation is not routinely used in adrenocortical carcinoma, in a retrospective observational study from a single center, the 3-year overall survival rate was 49% among 39 patients treated only with surgery and 78% among 39 matched patients treated with radiation to the pituitary tumor bed after resection.[103]

Prognosis, Morbidity, and Mortality

Return of the hypothalamic-pituitary-adrenal axis function to normal after curative surgery varies according to the etiology of the disorder. For example, time to normalization of hormone levels was a median of 0.6 years for those with ectopic Cushing syndrome, a median of 1.4 years for patients with Cushing disease, and a median of 2.5 years for patients with adrenal Cushing syndrome.[104] Recurrence of hypercortisolemia after curative treatment with transsphenoidal surgery occurred in up to 35% of patients with Cushing disease and more rarely in those with ectopic Cushing syndrome and bilateral adrenal disease after unilateral adrenal surgery.[105]

Sustained hypercortisolemia can lead to psychiatric disorders such as depression and anxiety disorders. Other consequences of hypercortisolemia include diabetes, hypertension, hypercoagulopathy,[106] hypokalemia, infections,[107] dyslipidemia, skeletal fragility or osteoporosis,[108] poor physical fitness, and proximal myopathy.[36,44,109] Additionally, patients with Cushing disease can also have hypogonadism, growth hormone deficiency, and central hypothyroidism.[8,9,22,110] In a Swedish registry study of 502 patients with Cushing disease, the standardized incidence rate for several complications was high within a 3-year period before the diagnosis: myocardial infarction, 4.4 (95% CI, 1.2-1.4); fractures, 4.9 (95% CI, 2.7-8.3); and deep vein thrombosis, 13.8 (95% CI, 3.8-35.3).[111]

Mortality is increased in patients with endogenous Cushing syndrome even after remission.[112-114] In a meta-analysis of 14 articles including 3691 patients, the number of deaths reported was 3-fold higher than the expected number of deaths in an age- and sex-matched population (standardized mortality ratio, 3.0 [95% CI, 2.3-3.9; I^2 = 80.5%]; absolute rates not provided).[115] In a separate analysis of 87 articles including 19 181 patients, atherosclerotic disease, thromboembolism, and infection were the cause of death among 56% of patients.[115]

Limitations

This review has several limitations. First, article quality was not formally evaluated. Second, few randomized clinical trials were available to inform treatment guidelines. Third, the literature search may have missed some relevant articles. Fourth, the literature search was limited to English-language articles. Fifth, some recommendations are based on expert opinion, which may be subject to bias.

Conclusions

The incidence of Cushing syndrome due to endogenous overproduction of cortisol is 2 to 8 per million people annually. First-line therapy for Cushing syndrome due to endogenous overproduction of cortisol is surgery to remove the underlying tumor. Many patients will require additional treatment with medications, radiation, or bilateral adrenalectomy.

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REFERENCES

1. Laugesen K, Jørgensen JOL, Petersen I, Sørensen HT. Fifteen-year nationwide trends in systemic glucocorticoid drug use in Denmark. *Eur J Endocrinol*. 2019;181(3):267-273. doi:10.1530/EJE-19-0305

2. Nieman LK, Biller BM, Findling JW, et al. The diagnosis of Cushing's syndrome: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2008;93(5):1526-1540. doi:10.1210/jc.2008-0125

3. Broder MS, Neary MP, Chang E, Cherepanov D, Ludlam WH. Incidence of Cushing's syndrome and Cushing's disease in commercially-insured patients <65 years old in the United States. *Pituitary*. 2015;18(3):283-289. doi:10.1007/s11102-014-0569-6

4. Tritos NA, Miller KK. Diagnosis and management of pituitary adenomas: a review. *JAMA*. 2023;329(16):1386-1398. doi:10.1001/jama.2023.5444

5. Valassi E, Santos A, Yaneva M, et al; ERCUSYN Study Group. The European Registry on Cushing's syndrome: 2-year experience. baseline demographic and clinical characteristics. *Eur J Endocrinol*. 2011;165(3):383-392. doi:10.1530/EJE-11-0272

6. Dekkers AJ, Amaya JM, van der Meulen M, Biermasz NR, Meijer OC, Pereira AM. Long-term effects of glucocorticoid excess on the brain. *J Neuroendocrinol*. 2022;34(8):e13142. doi:10.1111/jne.13142

7. Braun LT, Riester A, Oßwald-Kopp A, et al. Toward a diagnostic score in Cushing's syndrome. *Front Endocrinol (Lausanne)*. 2019;10:766. doi:10.3389/fendo.2019.00766

8. Fleseriu M, Auchus R, Bancos I, et al. Consensus on diagnosis and management of Cushing's disease: a guideline update. *Lancet Diabetes Endocrinol*. 2021;9(12):847-875. doi:10.1016/S2213-8587(21)00235-7

9. Hinojosa-Amaya JM, Varlamov EV, McCartney S, Fleseriu M. Hypercortisolemia recurrence in Cushing's disease; a diagnostic challenge. *Front Endocrinol (Lausanne)*. 2019;10:740. doi:10.3389/fendo.2019.00740

10. Braun LT, Vogel F, Zopp S, et al. Whom should we screen for Cushing syndrome? the Endocrine Society Practice guideline recommendations 2008 revisited. *J Clin Endocrinol Metab*. 2022;107(9):e3723-e3730. doi:10.1210/clinem/dgac379

11. Lindholm J, Juul S, Jørgensen JO, et al. Incidence and late prognosis of Cushing's syndrome: a population-based study. *J Clin Endocrinol Metab*. 2001;86(1):117-123. doi:10.1210/jc.86.1.117

12. Park JS, Yun SJ, Lee JK, Park SY, Chin SO. Descriptive epidemiology and survival analysis of prolactinomas and Cushing's disease in Korea. *Endocrinol Metab (Seoul)*. 2021;36(3):688-696. doi:10.3803/EnM.2021.1000

13. Ragnarsson O, Olsson DS, Chantzichristos D, et al. The incidence of Cushing's disease: a nationwide Swedish study. *Pituitary*. 2019;22(2):179-186. doi:10.1007/s11102-019-00951-1

14. Ragnarsson O, Olsson DS, Papakokkinou E, et al. Overall and disease-specific mortality in patients with Cushing disease: a Swedish nationwide study. *J Clin Endocrinol Metab*. 2019;104(6):2375-2384. doi:10.1210/jc.2018-02524

15. Bolland MJ, Holdaway IM, Berkeley JE, et al. Mortality and morbidity in Cushing's syndrome in New Zealand. *Clin Endocrinol (Oxf)*. 2011;75(4):436-442. doi:10.1111/j.1365-2265.2011.04124.x

16. Valassi E. Clinical presentation and etiology of Cushing's syndrome: Data from ERCUSYN. *J Neuroendocrinol*. 2022;34(8):e13114. doi:10.1111/jne.13114

17. Rubinstein G, Osswald A, Hoster E, et al. Time to diagnosis in Cushing's syndrome: a meta-analysis based on 5367 patients. *J Clin Endocrinol Metab*. 2020;105(3):dgz136. doi:10.1210/clinem/dgz136

18. Zhou J, Zhang M, Bai X, et al. Demographic characteristics, etiology, and comorbidities of patients with Cushing's syndrome: a 10-year retrospective study at a large general hospital in China. *Int J Endocrinol*. 2019:7159696. doi:10.1155/2019/7159696

19. Melmed S. Pituitary-tumor endocrinopathies. *N Engl J Med*. 2020;382(10):937-950. doi:10.1056/NEJMra1810772

20. Hernández-Ramírez LC, Stratakis CA. Genetics of Cushing's syndrome. *Endocrinol Metab Clin North Am*. 2018;47(2):275-297. doi:10.1016/j.ecl.2018.02.007

21. Reincke M, Sbiera S, Hayakawa A, et al. Mutations in the deubiquitinase gene *USP8* cause Cushing's disease. *Nat Genet*. 2015;47(1):31-38. doi:10.1038/ng.3166

22. Lacroix A, Feelders RA, Stratakis CA, Nieman LK. Cushing's syndrome. *Lancet*. 2015;386(9996):913-927. doi:10.1016/S0140-6736(14)61375-1

23. Zennaro MC, Boulkroun S, Fernandes-Rosa F. Genetic causes of functional adrenocortical adenomas. *Endocr Rev*. 2017;38(6):516-537. doi:10.1210/er.2017-00189

24. Bouys L, Vaczlavik A, Jouinot A, et al. Identification of predictive criteria for pathogenic variants of primary bilateral macronodular adrenal hyperplasia (PBMAH) gene *ARMC5* in 352 unselected patients. *Eur J Endocrinol*. 2022;187(1):123-134. doi:10.1530/EJE-21-1032

25. Melmed S, Kaiser UB, Lopes MB, et al. Clinical biology of the pituitary adenoma. *Endocr Rev*. 2022;43(6):1003-1037. doi:10.1210/endrev/bnac010

26. Jagannathan J, Smith R, DeVroom HL, et al. Outcome of using the histological pseudocapsule as a surgical capsule in Cushing disease. *J Neurosurg*. 2009;111(3):531-539. doi:10.3171/2008.8.JNS08339

27. Lonser RR, Nieman L, Oldfield EH. Cushing's disease: pathobiology, diagnosis, and management. *J Neurosurg*. 2017;126(2):404-417. doi:10.3171/2016.1.JNS152119

28. Cristante J, Lefournier V, Sturm N, et al. Why we should still treat by neurosurgery patients with Cushing disease and a normal or inconclusive pituitary MRI. *J Clin Endocrinol Metab*. 2019;104(9):4101-4113. doi:10.1210/jc.2019-00333

29. Chen J, Jian X, Deng S, et al. Identification of recurrent *USP48* and *BRAF* mutations in Cushing's disease. *Nat Commun*. 2018;9(1):3171. doi:10.1038/s41467-018-05275-5

30. Wanichi IQ, de Paula Mariani BM, Frassetto FP, et al. Cushing's disease due to somatic *USP8* mutations: a systematic review and meta-analysis. *Pituitary*. 2019;22(4):435-442. doi:10.1007/s11102-019-00973-9

31. Davi' MV, Cosaro E, Piacentini S, et al. Prognostic factors in ectopic Cushing's syndrome due to neuroendocrine tumors: a multicenter study. *Eur J Endocrinol*. 2017;176(4):453-461. doi:10.1530/EJE-16-0809

32. Beuschlein F, Fassnacht M, Assié G, et al. Constitutive activation of PKA catalytic subunit in adrenal Cushing's syndrome. *N Engl J Med*. 2014;370(11):1019-1028. doi:10.1056/NEJMoa1310359

33. Mihai R. Diagnosis, treatment and outcome of adrenocortical cancer. *Br J Surg*. 2015;102(4):291-306. doi:10.1002/bjs.9743

34. Lerario AM, Mohan DR, Hammer GD. Update on biology and genomics of adrenocortical carcinomas: rationale for emerging therapies. *Endocr Rev*. 2022;43(6):1051-1073. doi:10.1210/endrev/bnac012

35. Cavalcante IP, Berthon A, Fragoso MC, et al. Primary bilateral macronodular adrenal hyperplasia: definitely a genetic disease. *Nat Rev Endocrinol*. 2022;18(11):699-711. doi:10.1038/s41574-022-00718-y

36. Pivonello R, Isidori AM, De Martino MC, Newell-Price J, Biller BM, Colao A. Complications of Cushing's syndrome: state of the art. *Lancet Diabetes Endocrinol*. 2016;4(7):611-629. doi:10.1016/S2213-8587(16)00086-3

37. Barker LA, Gout BS, Crowe TC. Hospital malnutrition: prevalence, identification and impact on patients and the healthcare system. *Int J Environ Res Public Health*. 2011;8(2):514-527. doi:10.3390/ijerph8020514

38. Gowing LR, Ali RL, Allsop S, et al. Global statistics on addictive behaviours: 2014 status report. *Addiction*. 2015;110(6):904-919. doi:10.1111/add.12899

39. Kessler RC, Birnbaum HG, Shahly V, et al. Age differences in the prevalence and co-morbidity of *DSM-IV* major depressive episodes: results from the WHO World Mental Health Survey Initiative.

Depress Anxiety. 2010;27(4):351-364. doi:10.1002/da.20634

40. Nieman LK. Cushing's syndrome: update on signs, symptoms and biochemical screening. *Eur J Endocrinol*. 2015;173(4):M33-M38. doi:10.1530/EJE-15-0464

41. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract*. 2010;87(1):4-14. doi:10.1016/j.diabres.2009.10.007

42. Afshin A, Forouzanfar MH, Reitsma MB, et al; GBD 2015 Obesity Collaborators. Health effects of overweight and obesity in 195 countries over 25 years. *N Engl J Med*. 2017;377(1):13-27. doi:10.1056/NEJMoa1614362

43. Reimondo G, Pia A, Allasino B, et al. Screening of Cushing's syndrome in adult patients with newly diagnosed diabetes mellitus. *Clin Endocrinol (Oxf)*. 2007;67(2):225-229. doi:10.1111/j.1365-2265.2007.02865.x

44. Reincke M. Cushing syndrome associated myopathy: it is time for a change. *Endocrinol Metab (Seoul)*. 2021;36(3):564-571. doi:10.3803/EnM.2021.1069

45. Nieman LK. Molecular derangements and the diagnosis of ACTH-dependent Cushing's syndrome. *Endocr Rev*. 2022;43(5):852-877. doi:10.1210/endrev/bnab046

46. Shimon I. Screening for Cushing's syndrome: is it worthwhile? *Pituitary*. 2015;18(2):201-205. doi:10.1007/s11102-015-0634-9

47. Chiodini I, Mascia ML, Muscarella S, et al. Subclinical hypercortisolism among outpatients referred for osteoporosis. *Ann Intern Med*. 2007;147(8):541-548. doi:10.7326/0003-4819-147-8-200710160-00006

48. Fassnacht M, Arlt W, Bancos I, et al. Management of adrenal incidentalomas: European Society of Endocrinology Clinical practice guideline in collaboration with the European Network for the Study of ADRENAL TUMORS. *Eur J Endocrinol*. 2016;175(2):G1-G34. doi:10.1530/EJE-16-0467

49. Nieman LK. Approach to the patient with an adrenal incidentaloma. *J Clin Endocrinol Metab*. 2010;95(9):4106-4113. doi:10.1210/jc.2010-0457

50. Zavatta G, Vicennati V, Altieri P, et al. Mild autonomous cortisol secretion in adrenal incidentalomas and risk of fragility fractures: a large cross-sectional study. *Eur J Endocrinol*. 2023;188(4):343-352. doi:10.1093/ejendo/lvad038

51. León-Justel A, Madrazo-Atutxa A, Alvarez-Rios AI, et al; Spanish CRISALIDA Study Group. A probabilistic model for Cushing's syndrome screening in at-risk populations: a prospective multicenter study. *J Clin Endocrinol Metab*. 2016;101(10):3747-3754. doi:10.1210/jc.2016-1673

52. Findling JW, Raff H. Diagnosis of endocrine disease: differentiation of pathologic/neoplastic hypercortisolism (Cushing's syndrome) from physiologic/non-neoplastic hypercortisolism (formerly known as pseudo-Cushing's syndrome). *Eur J Endocrinol*. 2017;176(5):R205-R216. doi:10.1530/EJE-16-0946

53. Elamin MB, Murad MH, Mullan R, et al. Accuracy of diagnostic tests for Cushing's syndrome: a systematic review and metaanalyses. *J Clin Endocrinol Metab*. 2008;93(5):1553-1562. doi:10.1210/jc.2008-0139

54. Kannankeril J, Carroll T, Findling JW, et al. Prospective evaluation of late-night salivary cortisol and cortisone by EIA and LC-MS/MS in suspected Cushing syndrome. *J Endocr Soc*. 2020;4(10):bvaa107. doi:10.1210/jendso/bvaa107

55. Galm BP, Qiao N, Klibanski A, Biller BMK, Tritos NA. Accuracy of laboratory tests for the diagnosis of Cushing syndrome. *J Clin Endocrinol Metab*. 2020;105(6):dgaa105. doi:10.1210/clinem/dgaa105

56. Young J, Haissaguerre M, Viera-Pinto O, Chabre O, Baudin E, Tabarin A. Management of endocrine disease: Cushing's syndrome due to ectopic ACTH secretion: an expert operational opinion. *Eur J Endocrinol*. 2020;182(4):R29-R58. doi:10.1530/EJE-19-0877

57. Genere N, Kaur RJ, Athimulam S, et al. Interpretation of abnormal dexamethasone suppression test is enhanced with use of synchronous free cortisol assessment. *J Clin Endocrinol Metab*. 2022;107(3):e1221-e1230. doi:10.1210/clinem/dgab724

58. Petersenn S. Biochemical diagnosis of Cushing's disease: screening and confirmatory testing. *Best Pract Res Clin Endocrinol Metab*. 2021;35(1):101519. doi:10.1016/j.beem.2021.101519

59. Petersenn S. Overnight 1 mg dexamethasone suppression test and 24 h urine free cortisol-accuracy and pitfalls when screening for Cushing's syndrome. *Pituitary*. 2022;25(5):693-697. doi:10.1007/s11102-022-01249-5

60. Raff H. Late night salivary cortisol in the diagnosis of neoplastic hypercortisolism (including cyclic Cushing's syndrome). *Pituitary*. 2022;25(5):698-700. doi:10.1007/s11102-022-01214-2

61. Newell-Price J, Nieman LK, Reincke M, Tabarin A. Endocrinology in the time of COVID-19: management of Cushing's syndrome. *Eur J Endocrinol*. 2020;183(1):G1-G7. doi:10.1530/EJE-20-0352

62. Sarlis NJ, Chanock SJ, Nieman LK. Cortisolemic indices predict severe infections in Cushing syndrome due to ectopic production of adrenocorticotropin. *J Clin Endocrinol Metab*. 2000;85(1):42-47. doi:10.1210/jc.85.1.42

63. Petersenn S, Newell-Price J, Findling JW, et al; Pasireotide B2305 Study Group. High variability in baseline urinary free cortisol values in patients with Cushing's disease. *Clin Endocrinol (Oxf)*. 2014;80(2):261-269. doi:10.1111/cen.12259

64. Yanovski JA, Cutler GB Jr, Chrousos GP, Nieman LK. Corticotropin-releasing hormone stimulation following low-dose dexamethasone administration. a new test to distinguish Cushing's syndrome from pseudo-Cushing's states. *JAMA*. 1993;269(17):2232-2238. doi:10.1001/jama.1993.03500170062035

65. Alexandraki KI, Kaltsas GA, Isidori AM, et al. The prevalence and characteristic features of cyclicity and variability in Cushing's disease. *Eur J Endocrinol*. 2009;160(6):1011-1018. doi:10.1530/EJE-09-0046

66. Ceccato F, Tizianel I, Vedolin CK, Boscaro M, Barbot M, Scaroni C. Human corticotropin-releasing hormone tests: 10 years of real-life experience in pituitary and adrenal disease. *J Clin Endocrinol Metab*. 2020;105(11):dgaa564. doi:10.1210/clinem/dgaa564

67. Chen S, Chen K, Wang S, et al. The optimal cut-off of BIPSS in differential diagnosis of ACTH-dependent Cushing's syndrome: is stimulation necessary? *J Clin Endocrinol Metab*. 2020;105(4):dgz194. doi:10.1210/clinem/dgz194

68. Valassi E, Franz H, Brue T, et al; ERCUSYN Study Group. Diagnostic tests for Cushing's syndrome differ from published guidelines: data from ERCUSYN. *Eur J Endocrinol*. 2017;176(5):613-624. doi:10.1530/EJE-16-0967

69. Ceccato F, Barbot M, Mondin A, Boscaro M, Fleseriu M, Scaroni C. Dynamic testing for differential diagnosis of ACTH-dependent Cushing syndrome: a systematic review and meta-analysis. *J Clin Endocrinol Metab*. 2022;13(108):e178-e188. doi:10.1210/clinem/dgac686

70. Frete C, Corcuff JB, Kuhn E, et al. Non-invasive diagnostic strategy in ACTH-dependent Cushing's syndrome. *J Clin Endocrinol Metab*. 2020;105(10):dgaa409. doi:10.1210/clinem/dgaa409

71. Sheth SA, Mian MK, Neal J, et al. Transsphenoidal surgery for cushing disease after nondiagnostic inferior petrosal sinus sampling. *Neurosurgery*. 2012;71(1):14-22. doi:10.1227/NEU.0b013e31824f8e2e

72. Varlamov E, Hinojosa-Amaya JM, Stack M, Fleseriu M. Diagnostic utility of Gallium-68-somatostatin receptor PET/CT in ectopic ACTH-secreting tumors: a systematic literature review and single-center clinical experience. *Pituitary*. 2019;22(5):445-455. doi:10.1007/s11102-019-00972-w

73. De Venanzi A, Alencar GA, Bourdeau I, Fragoso MC, Lacroix A. Primary bilateral macronodular adrenal hyperplasia. *Curr Opin Endocrinol Diabetes Obes*. 2014;21(3):177-184. doi:10.1097/MED.0000000000000061

74. Nieman LK, Biller BM, Findling JW, et al; Endocrine Society. Treatment of Cushing's syndrome: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2015;100(8):2807-2831. doi:10.1210/jc.2015-1818

75. Yang AB, Henderson F Jr, Schwartz TH. Surgical strategies in the treatment of MR-negative Cushing's Disease: a systematic review and treatment algorithm. *Pituitary*. 2022;25(4):551-562. doi:10.1007/s11102-022-01239-7

76. Petersenn S, Beckers A, Ferone D, et al. Therapy of endocrine disease: outcomes in patients with Cushing's disease undergoing transsphenoidal surgery: systematic review assessing criteria used to define remission and recurrence. *Eur J Endocrinol*. 2015;172(6):R227-R239. doi:10.1530/EJE-14-0883

77. Broersen LHA, Biermasz NR, van Furth WR, et al. Endoscopic vs microscopic transsphenoidal surgery for Cushing's disease: a systematic review and meta-analysis. *Pituitary*. 2018;21(5):524-534. doi:10.1007/s11102-018-0893-3

78. He X, Findling JW, Auchus RJ. Glucocorticoid withdrawal syndrome following treatment of endogenous Cushing syndrome. *Pituitary*. 2022;25(3):393-403. doi:10.1007/s11102-022-01218-y

79. Hochberg Z, Pacak K, Chrousos GP. Endocrine withdrawal syndromes. *Endocr Rev*. 2003;24(4):523-538. doi:10.1210/er.2001-0014

80. Marques JVO, Boguszewski CL. Medical therapy in severe hypercortisolism. *Best Pract Res Clin Endocrinol Metab*. 2021;35(2):101487. doi:10.1016/j.beem.2021.101487

81. Lezoche E, Guerrieri M, Crosta F, et al. Perioperative results of 214 laparoscopic adrenalectomies by anterior transperitoneal

approach. *Surg Endosc*. 2008;22(2):522-526. doi:10.1007/s00464-007-9555-7

82. Sommerey S, Foroghi Y, Chiapponi C, et al. Laparoscopic adrenalectomy—10-year experience at a teaching hospital. *Langenbecks Arch Surg*. 2015;400(3):341-347. doi:10.1007/s00423-015-1287-x

83. Bancos I, Hahner S, Tomlinson J, Arlt W. Diagnosis and management of adrenal insufficiency. *Lancet Diabetes Endocrinol*. 2015;3(3):216-226. doi:10.1016/S2213-8587(14)70142-1

84. Fassnacht M, Dekkers OM, Else T, et al. European Society of Endocrinology Clinical Practice Guidelines on the management of adrenocortical carcinoma in adults, in collaboration with the European Network for the Study of Adrenal Tumors. *Eur J Endocrinol*. 2018;179(4):G1-G46. doi:10.1530/EJE-18-0608

85. Debillon E, Velayoudom-Cephise FL, Salenave S, et al. Unilateral adrenalectomy as a first-line treatment of Cushing's syndrome in patients with primary bilateral macronodular adrenal hyperplasia. *J Clin Endocrinol Metab*. 2015;100(12):4417-4424. doi:10.1210/jc.2015-2662

86. Osswald A, Quinkler M, Di Dalmazi G, et al. Long-term outcome of primary bilateral macronodular adrenocortical hyperplasia after unilateral adrenalectomy. *J Clin Endocrinol Metab*. 2019;104(7):2985-2993. doi:10.1210/jc.2018-02204

87. Lowe KM, Young WF Jr, Lyssikatos C, Stratakis CA, Carney JA. Cushing syndrome in Carney complex: clinical, pathologic, and molecular genetic findings in the 17 affected mayo clinic patients. *Am J Surg Pathol*. 2017;41(2):171-181. doi:10.1097/PAS.0000000000000748

88. Castinetti F, Nieman LK, Reincke M, Newell-Price J. Approach to the patient treated with steroidogenesis inhibitors. *J Clin Endocrinol Metab*. 2021;106(7):2114-2123. doi:10.1210/clinem/dgab122

89. Gadelha M, Bex M, Feelders RA, et al. Randomized trial of osilodrostat for the treatment of Cushing disease. *J Clin Endocrinol Metab*. 2022;107(7):e2882-e2895. doi:10.1210/clinem/dgac178

90. Fleseriu M, Pivonello R, Elenkova A, et al. Efficacy and safety of levoketoconazole in the treatment of endogenous Cushing's syndrome (SONICS): a phase 3, multicentre, open-label, single-arm trial. *Lancet Diabetes Endocrinol*. 2019;7(11):855-865. doi:10.1016/S2213-8587(19)30313-4

91. Pivonello R, Zacharieva S, Elenkova A, et al. Levoketoconazole in the treatment of patients with endogenous Cushing's syndrome: a double-blind, placebo-controlled, randomized withdrawal study (LOGICS). *Pituitary*. 2022;25(6):911-926. doi:10.1007/s11102-022-01263-7

92. Pivonello R, Fleseriu M, Newell-Price J, et al; LINC 3 investigators. Efficacy and safety of osilodrostat in patients with Cushing's disease (LINC 3): a multicentre phase III study with a double-blind, randomised withdrawal phase. *Lancet Diabetes Endocrinol*. 2020;8(9):748-761. doi:10.1016/S2213-8587(20)30240-0

93. Fleseriu M, Newell-Price J, Pivonello R, et al. Long-term outcomes of osilodrostat in Cushing's disease: LINC 3 study extension. *Eur J Endocrinol*. 2022;187(4):531-541. doi:10.1530/EJE-22-0317

94. Fleseriu M, Auchus RJ, Greenman Y, et al. Levoketoconazole treatment in endogenous Cushing's syndrome: extended evaluation of clinical, biochemical, and radiologic outcomes. *Eur J Endocrinol*. 2022;187(6):859-871. doi:10.1530/EJE-22-0506

95. Colao A, Petersenn S, Newell-Price J, et al; Pasireotide B2305 Study Group. A 12-month phase 3 study of pasireotide in Cushing's disease. *N Engl J Med*. 2012;366(10):914-924. doi:10.1056/NEJMoa1105743

96. Lacroix A, Gu F, Gallardo W, et al; Pasireotide G2304 Study Group. Efficacy and safety of once-monthly pasireotide in Cushing's disease: a 12 month clinical trial. *Lancet Diabetes Endocrinol*. 2018;6(1):17-26. doi:10.1016/S2213-8587(17)30326-1

97. Pivonello R, De Leo M, Cozzolino A, Colao A. The treatment of Cushing's disease. *Endocr Rev*. 2015;36(4):385-486. doi:10.1210/er.2013-1048

98. Palui R, Sahoo J, Kamalanathan S, Kar SS, Selvarajan S, Durgia H. Effect of cabergoline monotherapy in Cushing's disease: an individual participant data meta-analysis. *J Endocrinol Invest*. 2018;41(12):1445-1455. doi:10.1007/s40618-018-0936-7

99. Mondin A, Manara R, Voltan G, et al. Pasireotide-induced shrinkage in GH and ACTH secreting pituitary adenoma: a systematic review and meta-analysis. *Front Endocrinol (Lausanne)*. 2022;13:935759. doi:10.3389/fendo.2022.935759

100. Fleseriu M, Biller BM, Findling JW, Molitch ME, Schteingart DE, Gross C; SEISMIC Study Investigators. Mifepristone, a glucocorticoid receptor antagonist, produces clinical and metabolic benefits in patients with Cushing's syndrome. *J Clin Endocrinol Metab*. 2012;97(6):2039-2049. doi:10.1210/jc.2011-3350

101. Mathieu D, Kotecha R, Sahgal A, et al. Stereotactic radiosurgery for secretory pituitary adenomas: systematic review and International Stereotactic Radiosurgery Society practice recommendations. *J Neurosurg*. 2021;136(3):801-812. doi:10.3171/2021.2.JNS204440

102. Makis W, McCann K, Riauka TA, McEwan AJ. Ectopic Corticotropin-producing neuroendocrine tumor of the pancreas treated with 177Lu dotatate induction and maintenance peptide receptor radionuclide therapy. *Clin Nucl Med*. 2016;41(1):50-52. doi:10.1097/RLU.0000000000000971

103. Gharzai LA, Green MD, Griffith KA, et al. Adjuvant radiation improves recurrence-free survival and overall survival in adrenocortical carcinoma. *J Clin Endocrinol Metab*. 2019;104(9):3743-3750. doi:10.1210/jc.2019-00029

104. Berr CM, Di Dalmazi G, Osswald A, et al. Time to recovery of adrenal function after curative surgery for Cushing's syndrome depends on etiology. *J Clin Endocrinol Metab*. 2015;100(4):1300-1308. doi:10.1210/jc.2014-3632

105. Braun LT, Rubinstein G, Zopp S, et al. Recurrence after pituitary surgery in adult Cushing's disease: a systematic review on diagnosis and treatment. *Endocrine*. 2020;70(2):218-231. doi:10.1007/s12020-020-02432-z

106. van Haalen FM, Kaya M, Pelsma ICM, et al; Endo-ERN Cushing and Thrombosis study group. Current clinical practice for thromboprophylaxis management in patients with Cushing's syndrome across reference centers of the European Reference Network on Rare Endocrine Conditions (Endo-ERN). *Orphanet J Rare Dis*. 2022;17(1):178. doi:10.1186/s13023-022-02320-x

107. Varlamov EV, Langlois F, Vila G, Fleseriu M. Management of endocrine disease: cardiovascular risk assessment, thromboembolism, and infection prevention in Cushing's syndrome: a practical approach. *Eur J Endocrinol*. 2021;184(5):R207-R224. doi:10.1530/EJE-20-1309

108. Mazziotti G, Frara S, Giustina A. Pituitary diseases and bone. *Endocr Rev*. 2018;39(4):440-488. doi:10.1210/er.2018-00005

109. Vogel F, Braun L, Rubinstein G, et al. Patients with low IGF-I after curative surgery for Cushing's syndrome have an adverse long-term outcome of hypercortisolism-induced myopathy. *Eur J Endocrinol*. 2021;184(6):813-821. doi:10.1530/EJE-20-1285

110. Shekhar S, McGlotten R, Auh S, Rother KI, Nieman LK. The hypothalamic-pituitary-thyroid axis in Cushing syndrome before and after curative surgery. *J Clin Endocrinol Metab*. 2021;106(3):e1316-e1331. doi:10.1210/clinem/dgaa858

111. Papakokkinou E, Olsson DS, Chantzichristos D, et al. Excess morbidity persists in patients with Cushing's disease during long-term remission: a Swedish nationwide study. *J Clin Endocrinol Metab*. 2020;105(8):dgaa291. doi:10.1210/clinem/dgaa291

112. Valassi E, Tabarin A, Brue T, et al. High mortality within 90 days of diagnosis in patients with Cushing's syndrome: results from the ERCUSYN registry. *Eur J Endocrinol*. 2019;181(5):461-472. doi:10.1530/EJE-19-0464

113. Clayton RN, Jones PW, Reulen RC, et al. Mortality in patients with Cushing's disease more than 10 years after remission: a multicentre, multinational, retrospective cohort study. *Lancet Diabetes Endocrinol*. 2016;4(7):569-576. doi:10.1016/S2213-8587(16)30005-5

114. Bengtsson D, Ragnarsson O, Berinder K, et al. Increased mortality persists after treatment of Cushing's disease: a matched nationwide cohort study. *J Endocr Soc*. 2022;6(6):bvac045. doi:10.1210/jendso/bvac045

115. Limumpornpetch P, Morgan AW, Tiganescu A, et al. The effect of endogenous Cushing syndrome on all-cause and cause-specific mortality. *J Clin Endocrinol Metab*. 2022;107(8):2377-2388. doi:10.1210/clinem/dgac265