BMJ Best Practice

Cushing syndrome

Straight to the point of care

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Summary

Cushing syndrome is the clinical manifestation of pathological hypercortisolism from any cause.

Exogenous corticosteroid exposure is the most common cause of Cushing syndrome. Cushing's disease, which is hypercortisolism caused by an adrenocorticotrophic hormone (ACTH)-secreting pituitary adenoma, is the most common cause of endogenous Cushing syndrome, and is responsible for 70% to 80% of cases.

It may be difficult to distinguish patients with mild Cushing syndrome from those with the metabolic syndrome (central obesity with insulin resistance, and hypertension). Features more specific to Cushing syndrome include proximal muscle weakness, supraclavicular fat pads, facial plethora, violaceous striae, easy bruising, and premature osteoporosis.

After excluding exogenous corticosteroid use, patients with suspected Cushing syndrome should be tested for hypercortisolism with one of three high-sensitivity tests (late-night salivary cortisol, 1 mg overnight low-dose dexamethasone suppression testing, or 24-hour urinary free cortisol).

At least one additional test should be performed to confirm hypercortisolism in patients with a positive initial screening test.

Once endogenous hypercortisolism is confirmed, plasma ACTH should be measured. If ACTH is suppressed, diagnostic testing should focus on the adrenal glands. If ACTH is not suppressed, pituitary or ectopic disease should be sought.

Surgical resection of the pituitary or adrenal adenoma that is causing hypercortisolism is the primary treatment of choice in the vast majority of patients with endogenous Cushing syndrome.

Definition

Cushing syndrome is the clinical manifestation of pathological hypercortisolism from any cause. Patients often display weight gain with central obesity, facial rounding and plethora, proximal muscle weakness, and thinning of the skin. They also develop metabolic complications including diabetes mellitus, dyslipidaemia, metabolic bone disease, and hypertension. Cushing syndrome can be caused by exogenous corticosteroid exposure, by adrenocorticotrophic hormone (ACTH)-secreting pituitary tumours (termed Cushing's disease), by autonomous adrenal cortisol overproduction, and, rarely, by ectopic ACTH-secreting tumours.[1]

Epidemiology

Cushing syndrome is relatively uncommon in the general population, with an incidence of 1.8 to 3.2 per million population per year.[11] However, studies of high-risk groups report a significantly greater prevalence.[8] Hypercortisolism has been reported in 0.5% to 1% of patients with hypertension, 2% to 3% of patients with uncontrolled diabetes, 5% to 10% of patients with adrenal masses, and 11% of patients with osteoporosis and vertebral fractures.[8] [12] [13] [14] [15] It is unclear if this increase in prevalence is due to higher-sensitivity testing, a greater recognition of disease in high-risk groups, or variability in the diagnostic criteria between historical and more-recent studies.

Cushing syndrome occurs 3 times more commonly in women than in men, and Cushing's disease (adrenocorticotrophic hormone-secreting pituitary tumour) has a 3:1 to 5:1 female-to-male predominance.[1] No ethnic disparities in prevalence have been identified. The majority of adults are diagnosed between the ages of 20 and 50 years, although it can occur at any age. Cushing syndrome in children is unusual but well documented.[1]

Exogenous corticosteroid exposure is the most common cause of Cushing syndrome, but no data exist as to the exact epidemiology of exogenous disease. All currently reported statistics include only patients with endogenous Cushing syndrome.

Aetiology

Exogenous corticosteroid exposure is the most common cause of Cushing syndrome.

The majority (70% to 80%) of patients with endogenous Cushing syndrome have adrenocorticotrophic hormone (ACTH)-secreting pituitary adenomas; however, only 10% of all pituitary adenomas secrete excessive ACTH.[8] [16] Silent corticotroph adenomas are immunopositive for ACTH, but clinically present as non-functioning adenomas. However, large adenomas can rarely become ACTH secreting and cause Cushing's disease.[17] A new gene, ubiquitin-specific protease 8, has been found to be frequently mutated in Cushing's disease.[18]

About 10% of patients with endogenous Cushing syndrome have adrenal adenomas with unregulated secretion of cortisol, but only 5% of all adrenal adenomas develop autonomous cortisol secretion.[8] [14] Mutations in the cAMP/PKA pathway are the cause of most cases of primary adrenal hypercortisolism.[19] No specific exposures or modifiable factors have been identified that cause endogenous hypercortisolism. The aetiology of pituitary adenoma overproduction of ACTH and adrenal adenoma overproduction of cortisol is poorly understood.

Only about 1% of patients with Cushing syndrome have adrenal carcinoma. On the other hand, adrenal overproduction of cortisol is seen in 50% to 60% of adrenal carcinomas, resulting in ACTH-independent Cushing syndrome.[10]

Pathophysiology

The clinical manifestations result from excess tissue exposure to cortisol. The degree to which symptoms manifest is largely, if not entirely, based on the degree of cortisol excess. Patients with mild to moderate hypercortisolism generally have a less prominent phenotype with glucose intolerance, dyslipidaemia, metabolic bone disease, and abnormal weight gain, but are difficult to differentiate from other patients

with the metabolic syndrome. As the hypercortisolism increases, physical features worsen with striae, supraclavicular fat pads, and proximal muscle weakness developing. Ectopic adrenocorticotrophic hormone (ACTH) secretion from neuroendocrine tumours may manifest as more-severe cases with the abrupt presentation of symptoms and greatly elevated cortisol and ACTH. These patients may also have severe muscle weakness and weight loss.

Classification

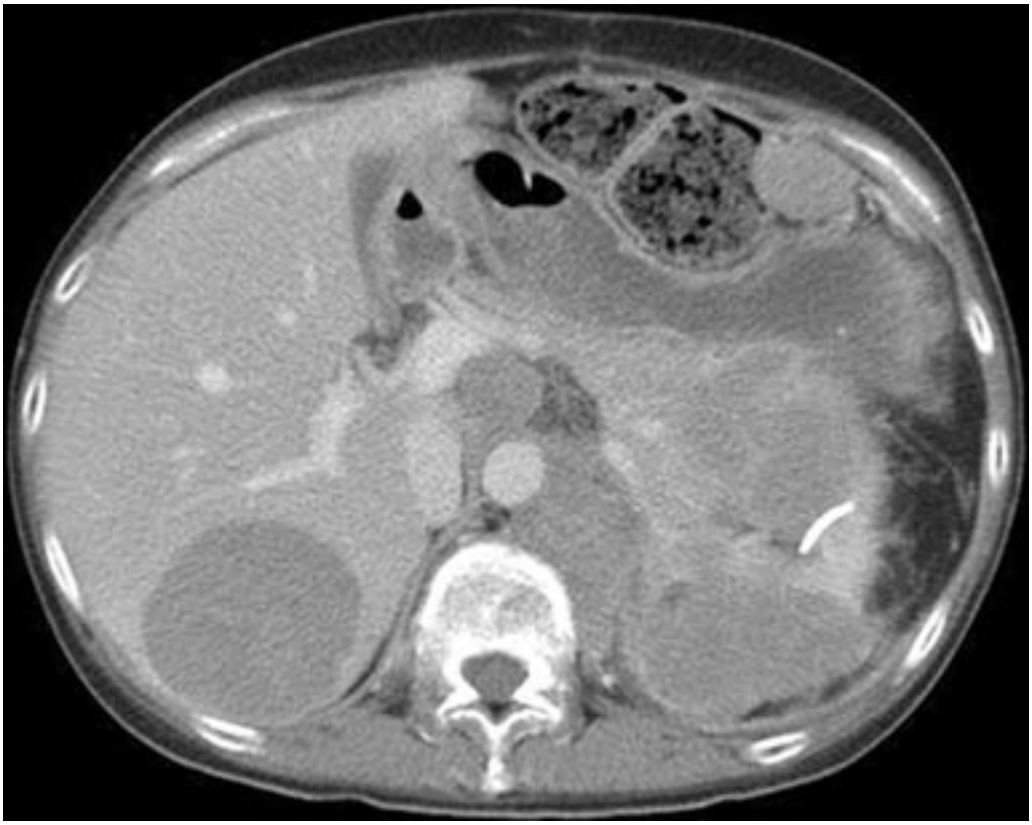
Aetiologies of hypercortisolism

Adrenocorticotrophic hormone (ACTH)-dependent

- Caused by conditions that have high or inappropriately normal ACTH levels stimulating adrenal cortisol overproduction.
- ACTH-secreting pituitary adenomas (Cushing's disease) and ectopic ACTH-secreting tumours are two forms of ACTH-dependent disease. Ectopic ACTH-secreting tumours are typically of bronchogenic or neuroendocrine origin.
- Ectopic corticotrophin-releasing hormone can be considered in this category, but is extremely rare and is not specifically discussed in detail here.

ACTH-independent

- ACTH-independent Cushing syndrome is caused by excessive cortisol secretion by the adrenal glands despite a suppressed ACTH level. Included in this category are adrenal adenomas, bilateral adrenal hyperplasia, and, rarely, adrenal carcinoma. Adrenal carcinoma is extremely rare and typically presents as a large (>5 cm) and rapidly growing adrenal mass.



Abdominal computed scan showing adrenocortical tumour infiltrating the pancreas and left kidney, and metastasised to the liver, spleen, and central nodes

From BMJ Case Reports 2010; doi:10.1136/bcr.07.2009.2100

- ACTH-independent bilateral macronodular adrenal hyperplasia (AIMAH) is a rare form of bilateral nodular adrenal disease. The pathophysiology of AIMAH is aberrant receptor stimulation. At least 10 different aberrant receptors causing AIMAH have been identified. They include gastric inhibitory polypeptide receptor, beta-adrenergic receptors, vasopressin receptor, serotonin receptor, angiotensin II receptor, luteinising hormone/human chorionic gonadotrophin receptor, and leptin receptor.[2] Stimulation of these receptors leads to inappropriate growth of bilateral, large, monoclonal and polyclonal nodules.[3] [4] Clinically, AIMAH presents most commonly in the fifth and sixth decades of life with excess glucocorticoid and mineralocorticoid production.[5] On imaging, bilaterally massively enlarged adrenal glands are seen.
- Primary pigmented nodular adrenocortical disease (PPNAD), often part of Carney's complex (a multiple endocrine neoplasia syndrome characterised by lentigines, cardiac and cutaneous myxomas, and endocrine tumours; may be inherited in an autosomal-dominant manner), is a rare condition caused by numerous small, autonomously functioning adrenal nodules ranging in size from microscopic to 1 cm. On pathological examination the nodules are darkly pigmented, and the intervening adrenal cortex is atrophic. Mutations in the protein kinase A type 1 alpha regulatory subunit (PRKAR1A) are believed to be the causative mutations. PPNAD has a bimodal age of distribution, with most cases being diagnosed in the second and third decades of life.[6] Patients with PPNAD tend to be rather lean, and present without the typical central obesity seen in other causes of Cushing syndrome. Severe osteoporosis, short stature, and severe muscle wasting are common presenting features of patients with PPNAD.[7]

Exogenous

- Patients taking exogenous corticosteroids for any reason may develop features of Cushing syndrome. When high-dose glucocorticosteroids are stopped, patients can develop adrenal insufficiency despite a clinical phenotype of Cushing's.

Case history

Case history #1

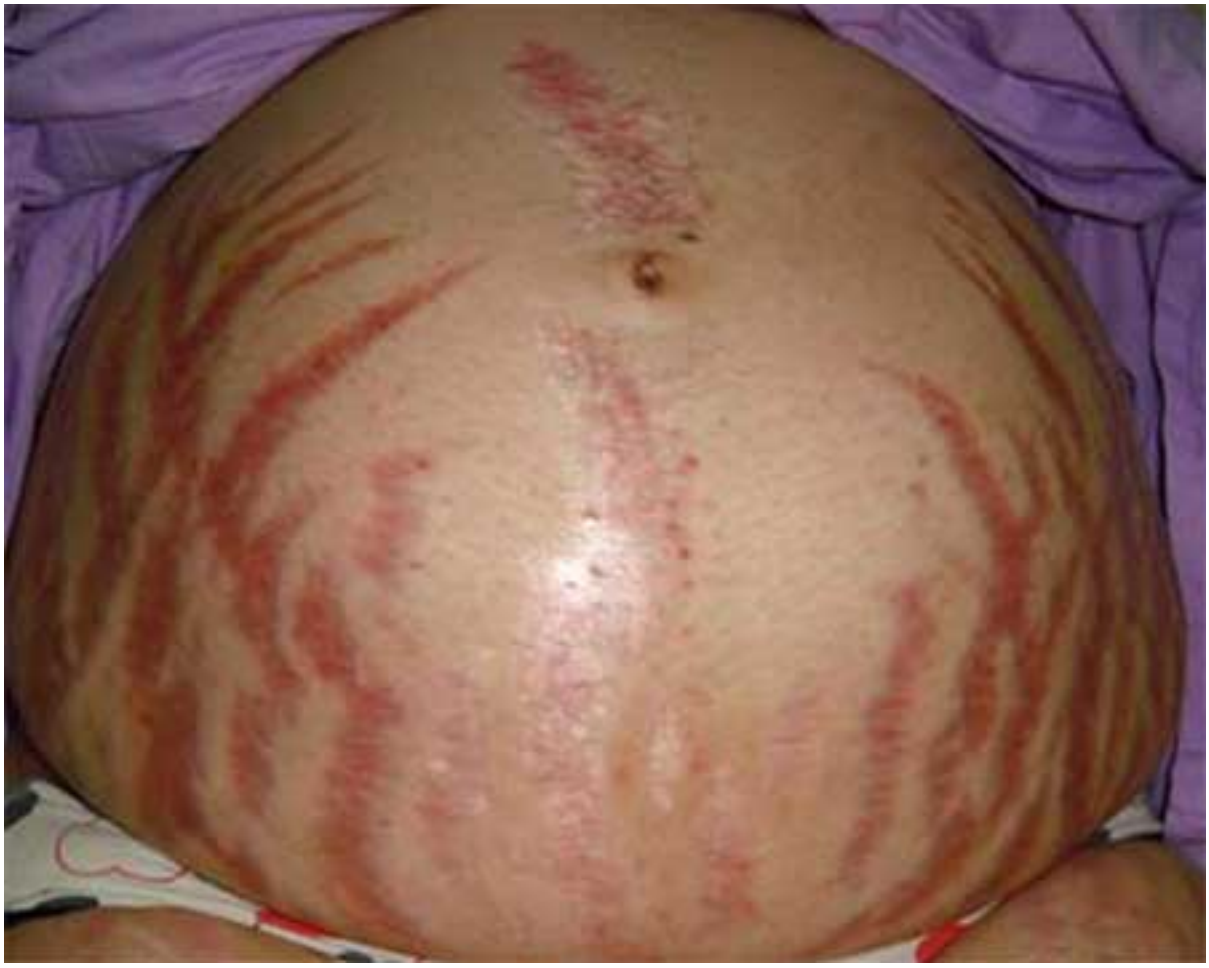
A 34-year-old woman presents with complaints of weight gain and irregular menses for the last several years. She has gained 20 kg over the past 3 years and feels that most of the weight gain is in her abdomen and face. She notes bruising without significant trauma, difficulty rising from a chair, and proximal muscle wasting. She was diagnosed with type 2 diabetes and hypertension 1 year ago.

Case history #2

A 54-year-old man presents for evaluation of an incidentally discovered adrenal nodule. He underwent a computed tomography scan of the abdomen for evaluation of abdominal pain, which was negative except for a 2 cm well-circumscribed, low-density (2 Hounsfield units) nodule in the right adrenal gland. He reports weight gain of 15 kg over the past 4 years. He has difficult-to-control type 2 diabetes and hypertension. He has had two episodes of renal colic in the last 5 years.

Other presentations

Cushing syndrome presents with a variety of non-specific signs and symptoms. Several features have higher specificity, such as violaceous striae, easy bruising, facial plethora, proximal muscle weakness, and unexplained osteoporosis.[8] [9] Presentation largely depends on the degree of hypercortisolism. Patients with severe and prolonged hypercortisolism develop more severe manifestations and complications. Patients with Cushing syndrome caused by the ectopic adrenocorticotrophic hormone syndrome generally have higher cortisol levels, and may develop severe muscle wasting, profound hypokalaemia, excessive striae, and severe hyperglycaemia. Additionally, rapid virilisation in females (rapid-onset or increased hirsutism, voice deepening, and clitoral enlargement) in the setting of cortisol excess suggest adrenal carcinoma.[10] Cushing syndrome in pregnancy may be difficult to diagnose due to overlapping features with pre-eclampsia and gestational diabetes, so it is important to have a high index of suspicion. Pregnant patients may present with features such as weight gain, hypertension, easy bruisability, violaceous striae, extremity oedema, and hirsutism. A common presentation in children is growth deceleration with accompanying weight gain. Less common clinical features include multiple renal stones, osteoporosis in younger people, or hypokalaemia without other features suggestive of Cushing syndrome.



Abdominal striae in pregnancy

From BMJ Case Reports 2011; doi:10.1136/bcr.01.2011.3720

Approach

The most important decision in the diagnosis of Cushing syndrome is deciding which patients need to begin a diagnostic evaluation. With the growing epidemic of obesity and metabolic syndrome (central obesity with hypertension and insulin resistance), many patients have a Cushingoid phenotype, but most do not have Cushing syndrome.

Important considerations include female sex, as women have a higher proportion of Cushing syndrome, unexplained hypertension (particularly in young patients), new onset of glucose intolerance or diabetes, unexplained weight gain, unexplained fractures (due to premature osteoporosis), hirsutism, menstrual irregularities, and unexplained proximal muscle weakness. Cushing syndrome creates a hypercoagulable state and is associated with an increased risk of venous thromboembolic disease, such as deep vein thrombosis and pulmonary embolism.[1]

History

All patients with suspected Cushing syndrome should have a complete history to exclude the use of oral, injectable, inhaled, or topical glucocorticoids manifesting as iatrogenic disease. At a minimum, patients with the following conditions should go on to be screened:[23] [24]

- Features unusual for age (i.e., osteoporosis or hypertension in young patients)
- Less-usual features, such as unexplained psychiatric symptoms (including depression)
- Unexplained nephrolithiasis
- Multiple or progressive symptoms
- Polycystic ovary syndrome
- Pituitary adenomas
- Adrenal adenomas.[25]

Physical

Clinical features suggesting Cushing syndrome include:

- Progressive proximal muscle weakness
- Bruising without obvious trauma
- Facial plethora or rounding
- Violaceous striae
- Supraclavicular fat pad
- Dorsocervical fat pad.

Children exhibiting weight gain with linear decreased growth velocity should also be considered. In addition, many patients have increased frequency of acne on the face, back, and chest.

Rapid virilisation in females (rapid-onset or increased hirsutism, voice deepening, and clitoral enlargement) in the setting of cortisol excess suggest adrenal carcinoma, which is associated with a 50% to 60% chance of Cushing syndrome.[10]

Initial biochemical testing

One of the following three high-sensitivity tests, or a combination, should be used as a first-line diagnostic test in patients with suspected Cushing syndrome:[23] [26] [27]

- Late-night salivary cortisol

- Overnight 1 mg dexamethasone suppression testing
- 24-hour urinary free cortisol

The 48-hour 2 mg dexamethasone suppression test is rarely used in isolation but can be used in combination with other tests. Although all of the included diagnostic tests are highly sensitive and specific, dexamethasone suppression testing was found to be the most sensitive while 24-hour urinary free cortisol was less sensitive.[28]

Confirmation of biochemical testing

To increase diagnostic accuracy, the initial high-sensitivity test should be repeated.[23] For example, late-night salivary cortisol samples should be obtained on two separate nights.[29] [30] [31] Similarly, at least two 24-hour urinary free cortisol samples should be collected.[32] Alternatively, a second high-sensitivity test may be performed: for example, supplementing a late-night salivary cortisol test with a 24-hour urinary free cortisol measurement.[33] Testing of late-night salivary cortisol is more accurate at initial diagnosis, but late-night salivary cortisol can frequently be normal in patients with recurrent/persistent disease after pituitary surgery, requiring more samples for testing.[34]

Patients with initial normal biochemical testing are unlikely to have Cushing syndrome. If signs or symptoms progress, or intermittent Cushing syndrome is suspected, repeat biochemical testing can be performed after 6 months or at a time when cortisol hypersecretion is assumed.[23]

Patients with any abnormal initial biochemical testing require further investigation and referral to an endocrinologist should be considered. Before proceeding with any further evaluation, physiological causes of hypercortisolism should be excluded. These conditions include: psychiatric disorders including depression, alcohol use disorder, physical stress, malnutrition, pregnancy, and perhaps class III obesity (BMI 40 or above) or metabolic syndrome.[26] [35] [36] [37] Urine pregnancy testing should be considered to exclude pregnancy, and glucose testing may reveal concomitant glucose intolerance or diabetes.

If multiple additional tests are abnormal, the patient has Cushing syndrome and differential diagnostic testing should be undertaken. Greatly elevated dehydroepiandrosterone sulfate levels are suggestive of adrenocortical carcinoma, but are neither sensitive nor specific.

[Algorithm for diagnosis of Cushing syndrome] (https://staticweb.bmj.com/BP/CushingSyndrome/gr1_lrg.jpg) [26]

Initial differential diagnostic testing

Once hypercortisolism has been established, further testing to determine the aetiology should be sought.

Morning plasma adrenocorticotrophic hormone (ACTH) is the test of choice for differentiating ACTH-dependent from ACTH-independent Cushing syndrome. Suppressed ACTH levels (<1 picomol/L [<5 picograms/mL]) suggest ACTH-independent Cushing syndrome (although assays differ between different laboratories), and further investigations should include imaging of the adrenal glands to identify adrenal pathology causing hypercortisolism, such as an adenoma.

Unsuppressed ACTH levels (>4 picomol/L [>20 picograms/mL]) suggest ACTH-dependent Cushing syndrome (although assays differ between different laboratories).[1] Further investigations in such patients should include pituitary/sellar magnetic resonance imaging (MRI) to identify an ACTH-secreting pituitary adenoma. A spoiled-gradient echo 3D T1 sequence has been shown to have higher sensitivity than dynamic MRI for detecting and localising pituitary micro-adenomas in patients with Cushing syndrome.[38]

Patients with ACTH-dependent Cushing syndrome and an adenoma ≥10 mm on MRI should proceed to treatment. Some clinicians prefer additional biochemical confirmation with high-dose dexamethasone suppression testing before initiating surgical therapy.[39] The use of high-dose dexamethasone suppression testing is an area of debate because of its variable sensitivity and specificity.[40]

Inferior petrosal sinus sampling

Patients with ACTH-dependent Cushing syndrome have either Cushing's disease (90% to 95%) or ectopic ACTH production (5% to 10%). Those without definitive lesions on MRI should undergo inferior petrosal sinus sampling (IPSS); this should be carried out in a specialised centre because of potential patient risk.[26] Patients with adenomas 6-9 mm on MRI should have IPSS to confirm the diagnosis.[26] Up to 40% of patients with Cushing's disease will not have visible lesions on pituitary/sellar MRI. Patients without definitive lesions on MRI should also undergo inferior petrosal sinus sampling.[1] [41] IPSS is the only test with sufficient diagnostic accuracy to differentiate Cushing's disease from ectopic ACTH production.[42] [43] Patients with an IPSS central/peripheral gradient >2:1 or 3:1 after corticotrophin-releasing hormone (CRH) stimulation have Cushing's disease and can undergo therapy. Those without a gradient are likely to have ectopic ACTH production.[41]

Tests for ectopic ACTH syndrome

Patients without an IPSS central/peripheral gradient >2:1 or 3:1 after CRH stimulation should be investigated for ectopic ACTH secretion. This evaluation generally includes computed tomography (CT) scanning of the chest, abdomen, and pelvis to look for a tumour secreting ACTH. The most common tumours that secrete ACTH are bronchial or thymic carcinoids. Other neuroendocrine tumours include islet cell and medullary thyroid cancer.[43] An MRI of the chest may be helpful in selected cases; other imaging modalities such as fluorodeoxyglucose positron emission tomography, gallium-68 DOTATATE positron emission tomography/CT, and octreotide scanning may be considered in some patients.[44] [45] [46] [47] [48]

Mild autonomous Cushing syndrome

These patients have an incidentally discovered adrenal adenoma producing mildly excessive cortisol (previously known as subclinical Cushing syndrome). Mild cortisol excess requires a specialised approach and may be more difficult to diagnose as a function of the inherent nature of the disease.[49] In patients with incidentally discovered adrenal nodules without clinical features of Cushing syndrome, use the 1 mg dexamethasone suppression test as the initial diagnostic test because urinary free cortisol and late-night salivary cortisol have a lower sensitivity in these patients.[27] [50] [51][52]

One meta-analysis has shown that patients with bilateral adrenal incidentalomas present a higher prevalence of subclinical Cushing syndrome compared with patients with unilateral adrenal incidentalomas.[53]

History and exam

Key diagnostic factors

presence of risk factors (common)

- Key risk factors include exogenous corticosteroid use, pituitary or adrenal adenoma, or adrenal carcinoma.

facial plethora (common)

- Many patients with Cushing syndrome have plethora.[23] [61]

supraclavicular fullness (common)

- Increased subcutaneous fat in the supraclavicular fossa is commonly seen in patients. It is much less commonly seen in patients with obesity from other causes.

violaceous striae (common)

- Worsening or significant violaceous striae are commonly associated with hypercortisolism in younger individuals.[23] [61]

absence of pregnancy (common)

- Pregnancy should be excluded as a potential physiological cause of hypercortisolism.

menstrual irregularities (common)

- Women with hypercortisolism generally have irregular menses or amenorrhoea.

absence of malnutrition (common)

- Malnutrition should be excluded as a potential physiological cause of hypercortisolism.

absence of alcoholism (common)

- Alcoholism should be excluded as a potential physiological cause of hypercortisolism.

absence of physiological stress (common)

- States of physiological stress should be excluded as a potential cause of hypercortisolism.

linear growth deceleration in children (common)

- Almost all children (>95%) show decreasing linear growth velocity.[62] Decreasing linear growth with accompanying weight gain in children is suggestive of Cushing syndrome.[1]

Other diagnostic factors

female sex (common)

- Cushing syndrome has a female-to-male predominance of 3:1.[1]

hypertension (common)

- Among patients with hypertension, 0.5% to 1% have Cushing syndrome.[12] [13] However, hypertension is common, and most patients with hypertension do not have hypercortisolism.

glucose intolerance or diabetes mellitus (common)

- Up to 70% of Cushing syndrome patients have impairment of glucose metabolism (glucose intolerance, diabetes).[54] Patients with diabetes may have poorly controlled blood sugars. Poorly controlled diabetes is common, and only 2% to 3% of patients with poorly controlled diabetes have Cushing syndrome.[8] [55]

premature osteoporosis or unexplained fractures (common)

- Low bone density in younger men should raise suspicion.
- In patients with Cushing syndrome, osteoporosis occurs in over 50% and skeletal fractures in up to 76%.[56] As many as 11% of patients with osteoporosis and vertebral fractures have unsuspected hypercortisolism.[15]

weight gain and central obesity (common)

- Nearly all patients gain weight. The degree of weight gain is based on the severity and duration of hypercortisolism. The increasing prevalence of obesity in the general population has made weight gain a very non-specific finding. It has also made the decision about which patients to test more difficult.

acne (common)

- Many patients have increased frequency of acne on the face, back, and chest.

psychiatric symptoms (common)

- Mood changes are common and occur in 70% of patients with Cushing syndrome. Depression is the most common, but other psychiatric symptoms, such as anxiety and even psychosis, can also occur.[57] [58] These symptoms improve or resolve with effective treatment of the hypercortisolism.

decreased libido (common)

- Occurs in up to 90% of patients, and true gonadal dysfunction is common.[56] Men generally complain of decreased libido initially. As the hypercortisolism persists, erectile dysfunction may develop.

easy bruisability (common)

- Cushing syndrome patients have thinning of the skin and subcutaneous tissues with subsequent easy bruising.[23] [56] Bruising without obvious trauma is a relatively specific physical finding.

weakness (common)

- Muscle weakness is very common, with proximal weakness being most prominent.[1] [23] [56]

facial rounding (common)

- Rounding of the face occurs in most if not all people who are obese, giving this finding a low specificity for the diagnosis of Cushing syndrome. However, 90% of patients with Cushing syndrome develop this.

dorsocervical fat pads (common)

- Increased subcutaneous fat on the back of the neck is commonly seen in Cushing syndrome, but also in patients with obesity from other causes.

unexplained nephrolithiasis (uncommon)

- Some patients develop renal stones. Episodes of recurrent renal stones without other explanation should raise suspicion.

venothrombolic event (uncommon)

- Cushing syndrome creates a hypercoagulable state and is associated with an increased risk of venous thromboembolic disease.[1] Patients with Cushing syndrome have a 10-fold increased risk of venous thromboembolism (deep vein thrombosis, pulmonary embolism).[59] [60]

hirsutism (uncommon)

- Rapid onset of virilisation may be a sign of adrenal carcinoma, which is associated with a 50% to 60% chance of Cushing syndrome.[10]

Risk factors

Strong

exogenous corticosteroid use

- Patients who use any dose of exogenous glucocorticoid greater than the normal daily production by the adrenals are at risk for developing Cushing syndrome.[20] The exact dose and the duration needed to manifest Cushing syndrome varies among patients. Diagnosis of exogenous Cushing syndrome is obvious in the setting of treatment with high-dose glucocorticoids, with increased risk associated with higher daily and cumulative doses.[21] However, suspicion and detailed questioning may be required to determine glucocorticoid delivery via alternative routes (e.g., intra-articular, inhaled, topical therapy).[20]

pituitary adenoma

- About 70% to 80% of patients with Cushing syndrome have adrenocorticotrophic hormone-secreting pituitary adenomas (Cushing's disease).[8] However, up to 10% of the population has incidental pituitary lesions consistent with micro-adenomas.[22] The vast majority of these adenomas are non-secretory and do not cause Cushing's disease.

adrenal adenoma

- About 15% of patients with Cushing syndrome have adrenal adenomas that overproduce cortisol.[8] A significant proportion of patients with adrenal adenoma may have excess and inappropriate secretion of cortisol leading to mild cortisol excess, also known as subclinical Cushing syndrome.[8] [14]

adrenal carcinoma

- A very rare disease. When it does occur, it can cause adrenal overproduction of cortisol resulting in adrenocorticotrophic hormone-independent Cushing syndrome. About 50% to 60% of adrenal carcinomas present with Cushing syndrome, but only 1% of Cushing syndrome cases are caused by adrenal carcinoma.[10] Mixed Cushing and virilising syndromes are observed in the majority of patients, and cases may present with rapid onset of virilisation in women: for example, hirsutism, voice deepening, and clitoral enlargement.[10]

Weak

neuroendocrine tumours

- A small proportion of patients with Cushing syndrome have ectopic adrenocorticotrophic hormone (ACTH) secretion. Neuroendocrine tumours, especially of bronchial and thymic origin, are the most commonly reported to secrete excessive ACTH and cause ectopic ACTH syndrome.

thoracic or bronchogenic carcinoma

- These malignancies, especially small cell lung cancer, may produce adrenocorticotrophic hormone (ACTH) and cause the ectopic ACTH syndrome.

Investigations

1st test to order

Test	Result
urine pregnancy test • Women of childbearing potential should always have pregnancy excluded in the evaluation of hypercortisolism.	**negative**
serum glucose • Cushing syndrome commonly leads to diabetes and glucose intolerance.	**elevated**
late-night salivary cortisol • One of the first-line tests to consider in any patient with suspected Cushing syndrome.[26] • Samples are collected by saturating a collection swab with saliva or by passively drooling into a collection tube between 11 p.m. and midnight.[63] [64] • Obtaining multiple (at least two) samples may increase sensitivity, and initial testing should be performed with sampling on two separate nights.[23] [29] [30] [31] • Value greater than the upper limit of normal is considered positive. Normal values vary greatly depending on the assay and clinical laboratory used. • Positive results should be confirmed with dexamethasone suppression testing or 24-hour urinary free cortisol. • Testing of late-night salivary cortisol (LNSC) is more accurate at initial diagnosis, but LNSC can be frequently normal in patients with recurrent/persistent disease after pituitary surgery, thus sometimes more samples are needed.[34]	**elevated**
1 mg overnight dexamethasone suppression test • One of the first-line tests to consider in any patient with suspected Cushing syndrome.[26] • A positive test is defined as morning cortisol >50 nanomol/L (>1.8 micrograms/dL). • Should be a first-line test in any patient with suspected Cushing syndrome, except those taking medications affecting dexamethasone metabolism (phenytoin, carbamazepine, rifampin [rifampicin], and cimetidine). • Patient is given 1 mg of dexamethasone at 11 p.m., and a plasma cortisol level is obtained the following morning at 8 a.m. Dexamethasone levels are measured simultaneously with cortisol to ensure that appropriate levels are achieved. This may help in severely obese patients whose dexamethasone levels may be sub-optimal.[64] • Positive results should be confirmed with late-night salivary cortisol or 24-hour urinary free cortisol. • In patients with incidentally discovered adrenal nodules without clinical features of Cushing syndrome, the 1 mg dexamethasone suppression test should be the initial diagnostic test because urinary free cortisol and late-night salivary cortisol have a lower sensitivity in these patients.[50] [51]	**morning cortisol >50 nanomol/L (>1.8 micrograms/dL)**

Test	Result
24-hour urinary free cortisol • Normal ranges vary by assay method. • Should be considered as a possible first-line test in any patient with suspected Cushing syndrome, except those with renal failure. • Sensitivity may be lower than late-night salivary cortisol or 1 mg overnight dexamethasone suppression testing. • Patients need to be instructed on appropriate 24-hour urine collection, and should avoid excessive fluid intake.[23] • Likelihood ratio positive 10.6; likelihood ratio negative 0.16; diagnostic odds ratio 95.4.[64] • At least two 24-hour urinary free cortisol samples should be collected to increase diagnostic accuracy.[32] • Positive results should be confirmed with late-night salivary cortisol or 1 mg overnight dexamethasone suppression testing.	**>50 micrograms/24 hour**
48-hour 2 mg (low-dose) dexamethasone suppression test • Rarely used in isolation; used in combination with other tests. • A positive test is defined as morning cortisol >50 nanomol/L (>1.8 micrograms/dL). • May be considered as a first-line test in a patient with suspected Cushing syndrome, except those taking medications known to affect metabolism of dexamethasone.[23] Common examples of such medications include phenytoin, carbamazepine, rifampin (rifampicin), and cimetidine. • Patients should be given 0.5 mg of dexamethasone at 9 a.m. and at 6-hour intervals for 48 hours, with a plasma cortisol obtained at 9 a.m., 6 hours after the last dose.[39] [64] • Positive results should be confirmed with late-night salivary cortisol or 24-hour urinary free cortisol.	**morning cortisol >50 nanomol/L (>1.8 micrograms/dL)**

Other tests to consider

Test	Result
plasma dehydroepiandrosterone sulphate (DHEAS) level • Elevated plasma DHEAS level is not specific. However, in patients with accelerated virilisation and Cushingoid features, it may point to an adrenal carcinoma.	**elevated**
morning plasma adrenocorticotrophic hormone (ACTH) • Exercise caution in interpretation of values as assays differ between different laboratories, but typically values >4 picomol/L (>20 picograms/mL) suggest pituitary or ectopic source of disease.[1] Values <1 picomol/L (<5 picograms/mL) suggest adrenal source of disease. • Should be obtained only after biochemical diagnosis of hypercortisolism (Cushing syndrome) has been established. • If ACTH is not suppressed, ACTH-dependent Cushing's disease due to pituitary adenoma or Cushing's disease due to ectopic ACTH secretion is present. • Suppressed ACTH levels indicate ACTH-independent Cushing syndrome. • ACTH is unstable in blood samples at room temperature, and care must be taken to ensure appropriate handling of samples.	**>4 picomol/L (>20 picograms/mL) suggests pituitary or ectopic aetiology; <1 picomol/L (<5 picograms/mL) suggests adrenal aetiology**
pituitary MRI • Should be ordered as the initial imaging test in patients with confirmed adrenocorticotrophic hormone (ACTH)-dependent Cushing syndrome. • The majority of Cushing's disease adenomas measure <1 cm, and up to 40% of patients with Cushing's disease do not have an adenoma visible on MRI.[65] • Patients with ACTH-dependent Cushing syndrome and an adenoma ≥10 mm on MRI may proceed to treatment. Some clinicians prefer additional biochemical confirmation with high-dose dexamethasone suppression testing prior to initiating surgical therapy.[39] The use of high-dose dexamethasone suppression testing is an area of debate.[40]	**may show pituitary adenoma**
adrenal CT • Should be ordered as the initial imaging test in patients with confirmed adrenocorticotrophic hormone (ACTH)-independent Cushing syndrome. Several adrenal abnormalities can produce excess cortisol. However, solitary adrenal adenoma is by far the most common. • CT is very sensitive in detecting adrenal disease resulting in cortisol hypersecretion. • Patients with ACTH-independent Cushing syndrome and adrenal abnormality seen on CT can proceed to therapy.	**may show adrenal adenoma, hyperplasia, or tumour**
high-dose dexamethasone suppression test • Rarely used in some countries. Can be considered in patients together with inferior petrosal sinus sampling in differentiating pituitary versus ectopic source of adrenocorticotrophic hormone (ACTH)-dependent Cushing syndrome. • Patients should be given 2 mg of dexamethasone at 6-hour intervals for 48 hours, or as an overnight test using a single dose of 8 mg of dexamethasone at 11 p.m. Plasma cortisol should be obtained	**positive test is defined as suppression of cortisol <50% of the baseline value indicative of ACTH-dependent Cushing syndrome**

Test	Result
at the start of the test and on the following morning. A positive test suggests a pituitary source of ACTH oversecretion. However, the use of high-dose dexamethasone suppression testing is an area of debate because of its variable sensitivity and specificity.[40]	
inferior petrosal sinus sampling (IPSS) • Should be performed in patients with confirmed adrenocorticotrophic hormone (ACTH)-dependent Cushing syndrome without an obvious pituitary lesion on MRI or those with adenomas 6-9 mm in size on MRI.[1] [26][41] Should be carried out in a specialised centre because of potential patient risk.[26] IPSS is the only test with sufficient diagnostic accuracy to differentiate Cushing's disease from ectopic ACTH production.[42] [43] • Central/peripheral ACTH ratio >2:1 at baseline or >3:1 after corticotrophin-releasing hormone (CRH) stimulation. • Blood is sampled peripherally and in the inferior petrosal sinuses simultaneously. If the pituitary effluent (blood in the petrosal sinuses) has a concentration of ACTH greater than 2-fold that of peripheral blood at baseline or greater than 3-fold after stimulation with CRH, the source of the hypercortisolism is pituitary ACTH secretion.[41] • If the ACTH ratio does not reach this threshold, ectopic ACTH secretion is likely. • This is a technically demanding study that very few centres can perform well.	**elevated central/ peripheral ACTH ratio indicates pituitary source**
CT of chest, abdomen, and pelvis • Used to determine the source of ectopic adrenocorticotrophic hormone syndrome.	**may localise tumour**
MRI chest • May be helpful in selected cases of ectopic adrenocorticotrophic hormone syndrome to localise tumour.	**may localise tumour**
octreotide scanning • May be helpful in selected cases of ectopic adrenocorticotrophic hormone syndrome to localise tumour.	**may localise tumour**
gallium-68 DOTATATE PET/CT • Dotatate scans may detect small neuroendocrine tumours causing ectopic adrenocorticotrophic hormone production.	**may localise tumour**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Obesity	• Usually lack facial plethora, unexplained bruising, proximal muscle weakness, violaceous striae, supraclavicular fullness, and osteoporotic fractures.[23]	• Normal late-night salivary cortisol, dexamethasone suppression testing, or 24-hour urinary free cortisol.
Metabolic syndrome	• Usually lack facial plethora, unexplained bruising, proximal muscle weakness, violaceous striae, supraclavicular fullness, and osteoporotic fractures.[23]	• Normal late-night salivary cortisol, dexamethasone suppression testing, or 24-hour urinary free cortisol.

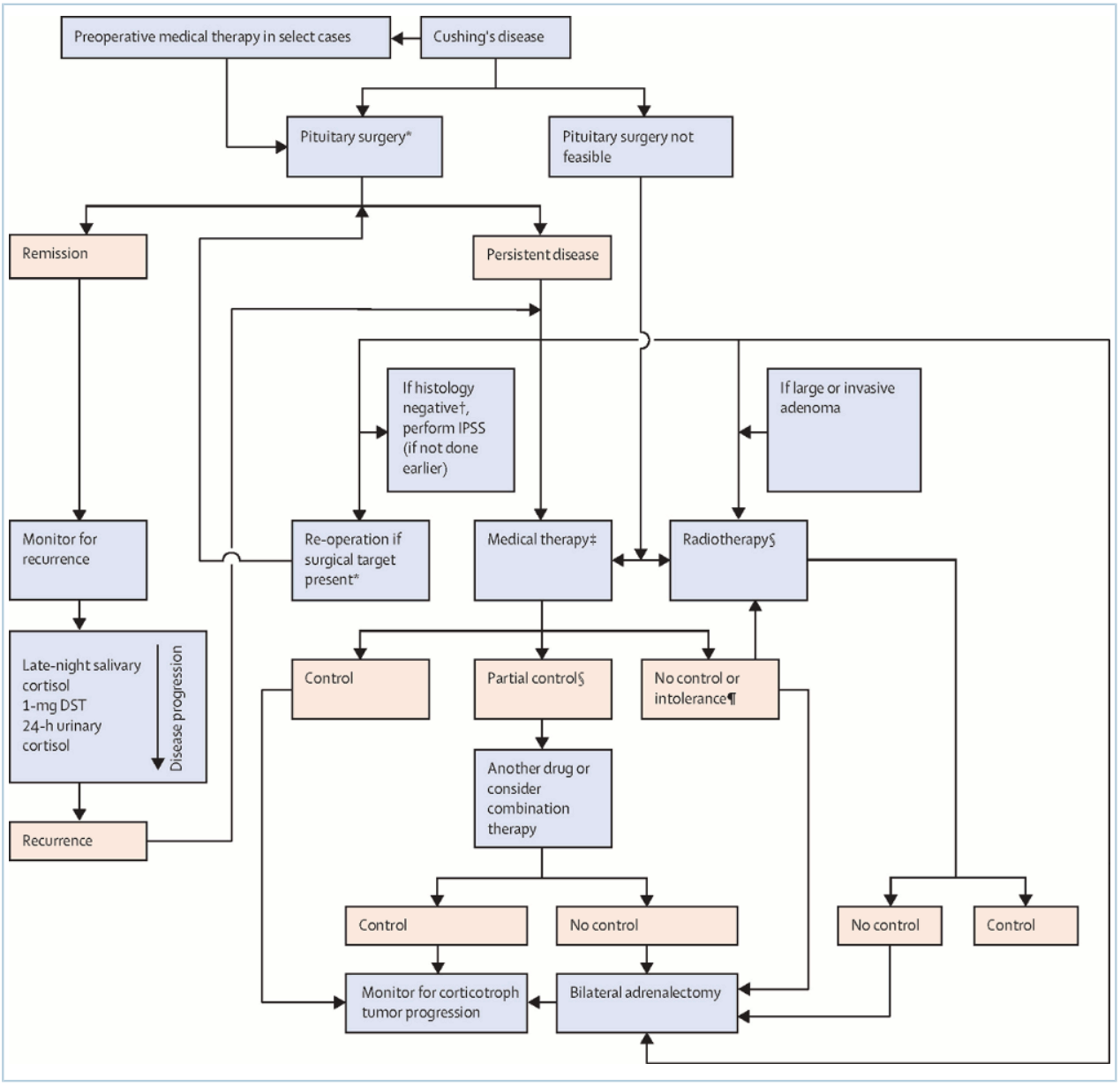
Approach

Do not start treatment until the diagnosis is firmly established and the source of hypercortisolism is recognised. Give patients with moderate to severe hypercortisolism therapy directed at the underlying cause. Resolution of cortisol excess in these cases has been shown to decrease mortality.[66] [67] Weigh up the potential benefits and risk of therapy options in patients with only mild cortisol excess (biochemical evidence of hypercortisolaemia but no clinical signs or symptoms of Cushing syndrome) because the benefit of surgery has not been definitively demonstrated.[51] [52] [68]

Cushing's disease (pituitary adenoma)

Cushing's disease is caused by adrenocorticotrophic hormone (ACTH)-secreting pituitary tumours. The ultimate goal of therapy is to remove the causative pituitary adenoma and normalise cortisol levels while preserving pituitary function.

First-line therapy is transsphenoidal (TSS) resection of the causative pituitary adenoma performed by an experienced surgeon.[26] [66] [69] Surgery can be done using an endoscopic or microscopic approach. Results are comparable between both techniques for microadenomas.[70] Whether there is potential incremental benefit with an endoscopic approach for macroadenomas remains unclear.[26] [70]



*Algorithm for the treatment of Cushing's disease (DST = dexamethasone suppression test. IPSS = inferior petrosal sinus sampling. ACTH = adrenocorticotrophic hormone. *Pituitary surgery should be performed by an experienced surgeon. †Absence of ACTH-staining adenoma. §Lifelong monitoring for hypopituitarism and secondary neoplasia in the radiation field required. ¶On maximum tolerated dose of the drug)*

Fleseriu M et al. Lancet Diabetes Endocrinol. 2021 Dec;9(12):847-75; used with permission

Many patients are supported with corticosteroids following pituitary surgery but should be assessed for remission during the first postoperative week.[68] This is done by measuring morning cortisol at least 24 hours after the last dose of corticosteroid therapy. Patients with a postoperative morning cortisol of <55 nanomol/L (<2 micrograms/dL) are considered to be in remission and can transition into long-term follow-up. Patients with a postoperative morning cortisol of >138 nanomol/L (>5 micrograms/dL) require further evaluation and possibly further therapy. Patients with a morning cortisol between 55 and 138 nanomol/L (2 and 5 micrograms/dL) should be followed with additional measurements to detect a drop in subsequent morning cortisol levels. Individuals with morning cortisols >55 nanomol/L (>2 micrograms/dL) after surgery are 2.5 times more likely to have recurrences than those with cortisol levels <55 nanomol/L (<2 micrograms/dL).[71] [72] [73]

Postoperative hypocortisolism is predictive of remission, hence some centres advocate withholding routine corticosteroid therapy after pituitary surgery and monitoring cortisol levels every 8 hours or if symptoms of adrenal insufficiency occur.[74] If adrenal insufficiency occurs or low cortisol levels are documented, corticosteroid therapy is initiated. Other centres begin routine corticosteroid therapy immediately after surgery and evaluate for remission of hypercortisolism later in the postoperative course.[75] Corticosteroids are usually rapidly tapered to physiological doses within 1 week or less (often by discharge from hospital). Testing to see if the hypothalamic-pituitary-adrenal (HPA) axis has recovered can be done in follow-up by 3 months after surgery. Testing is usually a morning cortisol prior to the patient taking the morning hydrocortisone dose, if hydrocortisone therapy had been continued. Cortisol levels of >552 nanomol/L (>20 micrograms/dL) indicate recovery of the axis. Levels <83 nanomol/L (<3 micrograms/dL) indicate a continued need for corticosteroids. Levels between 83 nanomol/L (3 micrograms/dL) and 552 nanomol/L (20 micrograms/dL) should prompt further testing (cosyntropin stimulation testing, insulin tolerance testing, or metyrapone testing). Once recovery of HPA axis has been established, patients need to undergo testing for possible recurrence. Salivary cortisol testing seems to be a better predictor of early recurrence.[73] [76]

Additional therapy should be considered in patients with failure of initial pituitary surgery or with recurrence of disease. The incidence of recurrence in Cushing's disease is high, with 50% of recurrences occurring during the first 50 months after first surgery.[77] Standard therapies include repeat pituitary surgery, radiotherapy, bilateral adrenalectomy, or medical therapy.[69] [78]

Success rates of these treatment options vary between 25% (for some of the medical therapies) and 100% (bilateral adrenalectomy). Treatment options have specific advantages, limitations, and side-effects so treatment decisions should be individualised according to the specific needs of the patient and risk of complications.[77] [79]

Re-operation is frequently the preferred therapy if initial surgery fails. It should be considered in all patients with recurrence or persistence of disease. It is effective in about two-thirds of patients.[80] [81] [82] However, the risk of pituitary deficiency after re-operation is 50%. This is significantly higher than after initial surgical therapy.[80] If re-operation is ineffective, or if a patient is not a candidate for re-operation, another modality should be considered.

Radiotherapy by conventional fractionated radiotherapy or stereotactic radiosurgery is most commonly used in patients with persistent hypercortisolism after incomplete corticotroph tumour resection, particularly if the tumour is aggressive or invasive or considered unresectable.[26] Radiotherapy allows for control of hypercortisolism within 3 to 5 years in over half of patients.[83] [84] [85] [86] [87] This modality is perhaps best used as part of the therapy for patients with mild residual hypercortisolism, as full effects of therapy can take several years to be realised. Radiation of tumours located close to the optic chiasm increases the risk of damage to the optic chiasm, and this risk should be considered prior to therapy. Hypopituitarism can also occur following radiotherapy and is another risk to consider prior to initiating therapy. The exact risk of hypopituitarism after conventional fractionated radiotherapy versus stereotactic radiosurgery is unclear, but they seem similar.

Patients with unsuccessful re-operation who manifest severe hypercortisolism should be evaluated for therapy with medical therapy, bilateral adrenalectomy, or a combination of these therapies. The advantage to these approaches is the rapid onset of decreased cortisol levels or blockade of cortisol action.

Medical treatment with a somatostatin analogue (pasireotide), a dopamine agonist (cabergoline), a steroidogenesis inhibitor (osilodrostat, ketoconazole, levoketoconazole, metyrapone, mitotane, and

etomidate), or a glucocorticoid receptor antagonist (mifepristone) has been increasingly used in clinical practice. Medical therapy is indicated to control cortisol secretion in patients with mild hypercortisolism, as a short term adjunct for severe hypercortisolism before other therapies are undertaken, preoperatively to bridge the time period until control of hypercortisolism is achieved by radiotherapy, in cases with persistent or recurrent hypercortisolism after surgery, or where surgery is declined or not feasible (e.g., high surgical risk, metastatic disease).[88] [89] [90] [91] However, there is a paucity of high-quality studies of medical therapy in Cushing's disease, and caution should be employed when comparing efficacy rates owing to the variability in study design and quality.[91] Individualise medical therapy for patients with Cushing's disease based on the clinical scenario, including the severity of hypercortisolism.[26] In patients with severe disease, treat aggressively to normalise cortisol concentrations (or cortisol action). Use multiple serial tests of both urinary free cortisol and late-night salivary cortisol to monitor treatment outcomes.

- Pasireotide is a somatostatin analogue that selectively targets somatostatin receptors in corticotroph adenomas and is now being used to medically treat Cushing's disease.[89] [90] Pasireotide binds to a wide variety of somatostatin receptors, but with greater affinity to receptor 5, which is predominantly expressed in patients with corticotroph adenomas. The use of the regular-release formulation of pasireotide has been shown to decrease cortisol levels in most patients with Cushing's disease, but only normalises cortisol levels in 25% of patients.[92] The long-acting formulation of pasireotide showed normalisation in approximately 40% of patients, but hyperglycaemia was noted in up to 80% of patients.[93] In one study, tumour shrinkage was noted in 62.5% of patients after 6 months of pasireotide treatment.[94] Salivary cortisol also decreased after treatment; thus, salivary cortisol may be a more convenient biomarker to follow in assessing response to treatment in patients with Cushing's disease.[95] One 10-year single-centre experience with pasireotide reported sustained biochemical and clinical benefit in about 60% of patients with Cushing's disease.[96] This is a pituitary-targeted therapy and should only be used in patients with hypercortisolism due to ACTH-secreting pituitary tumours.[97] There is a high risk of hyperglycaemia, which requires careful patient selection, and a risk of QTc prolongation.[26]
- Cabergoline, a dopamine agonist, has been used off-label in the treatment of Cushing's disease in some countries with limited results.[89] [90] [98]
- Steroidogenesis inhibitors (agents that decrease adrenal corticosteroid production, such as osilodrostat, ketoconazole, levoketoconazole, metyrapone, mitotane, and etomidate) can be used (though off-label in some countries, except osilodrostat) in the treatment of Cushing syndrome.[26] [89] [90]
    - Osilodrostat is a potent oral inhibitor of steroidogenesis (inhibits steroid 11-beta-hydroxylase) that is approved in the US for the treatment of Cushing's disease in patients where pituitary surgery is not an option or has not been curative, and in Europe and Japan for the treatment of endogenous Cushing syndrome.[26] [99] Osilodrostat rapidly reduces urinary free cortisol with associated improvements in clinical signs of hypercortisolism, and is generally well tolerated.[99] There is a risk of hypocortisolism, hypokalaemia, and QTc prolongation; careful monitoring for hyperandrogenism is needed in women.[26]
    - Ketoconazole has a relatively rapid onset of steroidogenesis inhibition. Ketoconazole may cause idiopathic severe liver injury and adrenal insufficiency.[90] [100] [101] If used, liver and adrenal function should be monitored before and during treatment. Its use requires expert guidance and is contraindicated in patients with liver disease.[101]
    - Levoketoconazole is an adrenal steroidogenesis inhibitor that is approved for treatment in the US.[102] [103] [104]

- Metyrapone provides rapid onset of inhibition and can be obtained for compassionate use in the US.
- Mitotane has adrenostatic and adrenolytic properties, but has delayed efficacy due to slow onset of action and a narrow therapeutic window.[90] It is rarely used for Cushing syndrome due to causes other than adrenal carcinoma.
- Etomidate is a potent adrenostatic agent with a rapid onset of action. It is used only in emergencies (e.g., hypercortisol-induced psychosis), and must be given intravenously.[90]

- Mifepristone, a glucocorticoid receptor antagonist, blocks the effect of cortisol at the receptor level and should be considered in patients who have clinical and metabolic derangements of continued hypercortisolism with hyperglycaemia and/or diabetes. The US Food and Drug Administration has approved mifepristone for the treatment of hyperglycaemia associated with Cushing syndrome in patients with type 2 diabetes mellitus. Cortisol and ACTH levels may increase with the use of mifepristone due to feedback inhibition.[105] As such, cortisol levels should not be used to guide therapy in patients treated with mifepristone.[106]

Bilateral adrenalectomy provides an immediate cure to any cause of endogenous hypercortisolism, at the expense of causing permanent adrenal insufficiency (requiring cortisol and mineralocorticoid replacement) and creating a risk of Nelson syndrome (corticotroph tumour growth after adrenalectomy). This progression can cause hyperpigmentation from excessive ACTH and intracranial compressive symptoms from growth of the tumour outside the sella. Newer laparoscopic methods of adrenalectomy allow for more rapid recovery and tolerability.[107] One meta-analysis of 37 studies (1320 patients, 82% with Cushing's disease, 13% with ectopic Cushing syndrome, and 5% with primary adrenal hyperplasia) showed that bilateral adrenalectomy is relatively safe and provides adequate success.[108] Although residual cortisol secretion due to accessory adrenal tissue or adrenal remnants was found in up to 34% of patients, less than 2% had a relapse of Cushing syndrome. Symptoms of hypercortisolism (e.g., hypertension, obesity, or depression) improved in the majority of the patients after bilateral adrenalectomy. The number of adrenal crises per 100 patient years was 9.3, and Nelson's syndrome occurred in 21% of the patients. Excess mortality within the first year after surgery suggests that intensive clinical care for patients after bilateral adrenalectomy is warranted.

For replacement of non-glucocorticoid pituitary hormones following pituitary surgery (any combination of deficiencies may occur):[109]

- Levothyroxine is used to achieve a free T4 in the upper half of the normal range. A thyroid-stimulating hormone should not be used to guide therapy.
- Testosterone therapy is used to achieve a testosterone level in the normal range.
- Women with an intact uterus taking oestrogen replacement also need 10 days of progestin each month in addition to oestrogen replacement therapy.
- Decision to treat with growth hormone should be individualised for each patient based on symptoms, benefits, and risk of therapy. Dose titration should occur every month to achieve clinical response (i.e., energy level, sense of well-being, and lean body mass) and an insulin-like growth factor 1 (IGF-1) level in the age-adjusted mid- to upper-normal range.
- Desmopressin is titrated to control symptomatic excessive urine output. This is based on patient preference. Serum sodium and symptoms are monitored periodically to evaluate adequacy of treatment.

ACTH-independent Cushing syndrome

The most common cause of adrenal cortisol overproduction is a unilateral autonomous adrenal adenoma. First-line therapy is almost always unilateral adrenalectomy of the affected adrenal gland. Laparoscopic

adrenalectomy is the preferred method in most cases. Removal of the affected adrenal gland is curative in all patients with unilateral adrenal disease. Adrenalectomy has a beneficial effect on cardiovascular risk factors in patients with subclinical Cushing syndrome overall and compared with conservative management.[110]

Rare causes of ACTH-independent disease generally cause bilateral adrenal disease from autonomous nodule formation or bilateral hyperplasia.[19] [89] In these cases first-line therapy generally requires bilateral adrenalectomy. Steroidogenesis inhibitor therapy (osilodrostat, ketoconazole, levoketoconazole, metyrapone, mitotane, and etomidate), or a glucocorticoid receptor antagonist (mifepristone) can be used for patients who wish to avoid bilateral adrenalectomy.[19] [90] [111] Osilodrostat rapidly reduces urinary free cortisol with associated improvements in clinical signs of hypercortisolism, and is generally well tolerated.[26] [99] Ketoconazole has a relatively rapid onset of steroidogenesis inhibition. Ketoconazole may cause severe liver injury and adrenal insufficiency. Its use requires expert guidance and is contraindicated in patients with liver disease. If used, liver and adrenal function should be monitored before and during treatment.[101] Levoketoconazole is an adrenal steroidogenesis inhibitor that is approved for treatment in the US.[102] [103] [104] Metyrapone provides rapid onset of inhibition. Mitotane has slow onset of action, has a narrow therapeutic window, and is generally only used in adrenal carcinoma.[69] Etomidate, used only in emergencies, has rapid onset but must be given intravenously.[69] Mifepristone blocks cortisol action, resulting in attenuation of cortisol effects.

Adrenal carcinoma is an exceedingly rare cause of ACTH-independent Cushing syndrome. First-line therapy in many patients is surgical resection; however, at the time of diagnosis the disease has often progressed beyond the point where surgical therapy is effective. The effectiveness of chemotherapy and adjunctive therapies in both early- and late-stage disease has shown mixed results in clinical trials; however, patients should be considered for treatment with mitotane and enrolment in clinical trials (if available).[10]

Ectopic ACTH syndrome

The optimal first-line therapy involves locating and surgically resecting the ACTH-producing tumour. Not infrequently, complete resection of these tumours is not possible. Where surgical resection is not possible, second-line therapies include a glucocorticoid receptor antagonist (mifepristone), steroidogenesis inhibitor therapy (osilodrostat, ketoconazole, levoketoconazole, metyrapone, mitotane, and etomidate), or bilateral adrenalectomy.[89] Bilateral adrenalectomy is definitive therapy, but patients with ectopic ACTH-producing tumours may have extremely severe hypercortisolism, and require reduction in cortisol before proceeding to surgery. In these cases, mifepristone or steroidogenesis inhibitor therapy can be used to lower cortisol levels in preparation for bilateral adrenalectomy. Osilodrostat rapidly reduces urinary free cortisol with associated improvements in clinical signs of hypercortisolism, and is generally well tolerated.[26] [99] Ketoconazole has a relatively rapid onset of steroidogenesis inhibition. Ketoconazole may cause severe liver injury and adrenal insufficiency. Its use requires expert guidance and is contraindicated in patients with liver disease. If used, liver and adrenal function should be monitored before and during treatment.[101] Levoketoconazole is an adrenal steroidogenesis inhibitor that is approved for treatment in the US.[102] [103] [104] Metyrapone provides rapid onset of inhibition. Mitotane has slow onset of action, has a narrow therapeutic window, and is generally only used in adrenal carcinoma.[69] Etomidate, used only in emergencies, has rapid onset but must be given intravenously.[69] Mifepristone blocks cortisol action, resulting in attenuation of cortisol effects.

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Ongoing (summary)		
Cushing's disease (adrenocorticotrophic hormone [ACTH]-secreting pituitary tumour)		
	1st	transsphenoidal pituitary adenomectomy
	adjunct	medical therapy before surgery
	adjunct	post-surgical corticosteroid replacement therapy
	adjunct	post-surgical pituitary hormone replacement therapy
	1st	medical therapy alone
	2nd	repeat transsphenoidal pituitary adenomectomy
	adjunct	medical therapy before surgery
	adjunct	post-surgical corticosteroid replacement therapy
	adjunct	post-surgical pituitary hormone replacement therapy
	2nd	medical therapy alone
	2nd	pituitary radiotherapy
	adjunct	medical therapy before radiotherapy
	adjunct	post-radiation corticosteroid replacement therapy
	adjunct	post-radiation pituitary hormone replacement therapy
	2nd	bilateral adrenalectomy
	plus	permanent post-surgical corticosteroid and mineralocorticoid replacement therapy
	adjunct	medical therapy before surgery
ectopic ACTH or corticotrophin-releasing hormone (CRH) syndrome		
	1st	surgical resection or ablation of tumour and metastases
	adjunct	medical therapy before surgery

Ongoing		(summary)
	adjunct	chemotherapy or radiotherapy for primary tumour
	2nd	bilateral adrenalectomy
	plus	permanent post-surgical corticosteroid and mineralocorticoid replacement therapy
	adjunct	medical therapy before surgery
	adjunct	chemotherapy or radiotherapy for primary tumour
	3rd	medical therapy only
	adjunct	chemotherapy or radiotherapy for primary tumour
ACTH-independent due to unilateral adrenal carcinoma or adenoma		
	1st	unilateral adrenalectomy or tumour resection
	adjunct	medical therapy before surgery
	adjunct	chemotherapy or radiotherapy for adrenal carcinoma
	2nd	medical therapy only
	adjunct	chemotherapy or radiotherapy for adrenal carcinoma
ACTH-independent due to bilateral adrenal disease (hyperplasia or adenoma)		
	1st	bilateral adrenalectomy
	plus	permanent post-surgical corticosteroid and mineralocorticoid replacement therapy
	adjunct	medical therapy before surgery
	2nd	medical therapy only

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Ongoing

Cushing's disease (adrenocorticotrophic hormone [ACTH]-secreting pituitary tumour)

1st **transsphenoidal pituitary adenomectomy**

» First-line therapy is transsphenoidal resection of the causative pituitary adenoma performed by an experienced surgeon.[26] [69] [112] Surgery can be done using an endoscopic or microscopic approach. Results are comparable between both techniques for microadenomas.[70] Whether there is potential incremental benefit with an endoscopic approach for macroadenomas remains unclear.[26] [70]

» Patients with mild cortisol excess (biochemical evidence of hypercortisolaemia but no clinical signs or symptoms of Cushing syndrome) should have therapy carefully weighed because benefit of surgery has not been convincingly demonstrated.[68]

adjunct **medical therapy before surgery**

Treatment recommended for SOME patients in selected patient group

Primary options

» osilodrostat: 2 mg orally twice daily initially, increase gradually according to response, maximum 60 mg/day

OR

» metyrapone: 0.5 to 1 g/day orally given in 3-4 divided doses initially, increase gradually according to response, maximum 6 g/day

OR

» ketoconazole: 200-600 mg/day orally given in 2-3 divided doses initially, increase gradually according to response, maximum 1600 mg/day given in 2-4 divided doses

OR

» levoketoconazole: 150 mg orally twice daily initially, increase gradually according to response, maximum 1200 mg/day

Ongoing

OR

» pasireotide: 0.3 to 0.9 mg subcutaneously twice daily; 10-40 mg intramuscularly every 4 weeks

OR

» cabergoline: consult specialist for guidance on dose

OR

» mifepristone: 300 mg orally once daily initially, increase gradually according to response, maximum 1200 mg/day

Secondary options

» mitotane: consult specialist for guidance on dose

Tertiary options

» etomidate: consult specialist for guidance on dose

» A somatostatin analogue (pasireotide), a dopamine agonist (cabergoline), a steroidogenesis inhibitor (osilodrostat, ketoconazole, levoketoconazole, metyrapone, mitotane, etomidate), or a glucocorticoid receptor antagonist (mifepristone) is occasionally used short term for severe hypercortisolism before other therapies are undertaken.[88] [89] [90] [91]

» Somatostatin analogue: pasireotide binds to a wide array of somatostatin receptors, with a much greater affinity for somatostatin receptor 5, which is predominantly expressed in corticotroph adenomas. Use of the regular-release formulation of pasireotide decreases cortisol in most patients, but normalises cortisol levels in only 25% of patients.[92] The long-acting formulation of pasireotide normalises cortisol levels in 40% of patients.[93] It causes hyperglycaemia in most patients. This is a pituitary-targeted therapy and should be used only in patients with hypercortisolism due to ACTH-secreting pituitary tumours.[97] There is a high risk of hyperglycaemia, which requires careful patient selection, and a risk of QTc prolongation.[26]

» Dopamine agonist: cabergoline has been used off-label in the treatment of Cushing's disease in some countries.[98]

Ongoing

» Steroidogenesis inhibitors: osilodrostat, ketoconazole, levoketoconazole, metyrapone, mitotane, and etomidate decrease adrenal corticosteroid production.[89] [90] [99] They should only be used by physicians familiar with their use. Osilodrostat is approved in the US and Europe for use in Cushing's disease. It is a potent, rapidly active steroid 11-beta-hydroxylase inhibitor and is generally well tolerated.[99] There is a risk of hypocortisolism, hypokalaemia, and QTc prolongation; careful monitoring for hyperandrogenism is needed in women.[26] Ketoconazole and metyrapone have a relatively rapid onset of steroidogenesis inhibition. Ketoconazole may cause idiopathic severe liver injury and adrenal insufficiency. Its use requires expert guidance and is contraindicated in patients with liver disease. If used, liver and adrenal function should be monitored before and during treatment.[100] [101] Levoketoconazole is an adrenal steroidogenesis inhibitor that is approved for treatment in the US.[102] [103] [104] Mitotane has slow onset of action and a narrow therapeutic window. It is rarely used for Cushing syndrome due to causes other than adrenal carcinoma. Etomidate is rarely used and is reserved for emergency situations only. It has rapid onset but must be given intravenously.[90]

» Glucocorticoid receptor antagonist: mifepristone blocks cortisol at the receptor level and attenuates the clinical and biochemical effects associated with elevation of cortisol. The US Food and Drug Administration has approved mifepristone for the treatment of hyperglycaemia associated with Cushing syndrome. It may be used for all forms of Cushing syndrome. Cortisol levels may increase during therapy with mifepristone due to feedback inhibition.[105] As such, cortisol levels should not be used to guide therapy in patients treated with mifepristone.[106]

» Patients should be monitored for development of adrenal insufficiency.

» Dose adjustment should be based on clinical symptoms, biochemical normalisation of 24-hour urinary free cortisol, and late-night salivary cortisol (with the exception of mifepristone, where use of cortisol as a marker will not be reliable).

adjunct **post-surgical corticosteroid replacement therapy**

Treatment recommended for SOME patients in selected patient group

Ongoing

Primary options

» hydrocortisone: 10-25 mg per metre square body surface area/day orally given in 2-3 divided doses; usual dose is a larger dose in the morning (10-15 mg) and a smaller dose in the late afternoon (5-10 mg)

» Patients who undergo pituitary adenomectomy may become temporarily or permanently dependent on physiological replacement of cortisol. It is necessary to monitor blood pressure, check for orthostatic symptoms, and assess general sense of energy or fatigue.

» As postoperative hypocortisolism is predictive of remission, some centres advocate withholding routine corticosteroid therapy after pituitary surgery and monitoring cortisol levels every 8 hours or if symptoms of adrenal insufficiency occur. If adrenal insufficiency occurs or low cortisol levels are documented, corticosteroid therapy should be initiated. Other centres begin routine corticosteroid therapy immediately after surgery and evaluate for remission of hypercortisolism later in the postoperative course.[75] This is done by measuring morning cortisol at least 24 hours after the last dose of corticosteroid therapy. Patients with a postoperative morning cortisol of <55 nanomol/L (<2 micrograms/dL) are considered to be in remission and can transition into long-term follow-up. Patients with a postoperative morning cortisol of >138 nanomol/L (>5 micrograms/dL) require further evaluation and possibly further therapy. Patients with a morning cortisol between 55 and 138 nanomol/L (2 and 5 micrograms/dL) should be followed with additional measurements to detect a drop in subsequent morning cortisol levels. Individuals with morning cortisols >55 nanomol/L (>2 micrograms/dL) after surgery are 2.5 times more likely to have recurrences than those with cortisol levels <55 nanomol/L (<2 micrograms/dL).[71] [72] [73]

» Corticosteroids are usually rapidly tapered to physiological doses within 1 week or less (often by discharge from hospital). Testing to see if the hypothalamic-pituitary-adrenal (HPA) axis has recovered can be done in follow-up by 3 months after surgery. Testing is usually a morning cortisol prior to the patient taking the morning hydrocortisone dose, if hydrocortisone therapy had been continued. Cortisol levels of >552 nanomol/L (>20 micrograms/dL) indicate recovery of the axis. Levels <83 nanomol/L (<3

Ongoing

micrograms/dL) indicate a continued need for corticosteroids. Levels between 83 nanomol/L (3 micrograms/dL) and 552 nanomol/L (20 micrograms/dL) should prompt further testing (cosyntropin stimulation testing, insulin tolerance testing, or metyrapone testing). Once recovery of HPA axis has been established, patients need to undergo testing for possible recurrence. Salivary cortisol testing seems to be a better predictor of early recurrence.[73] [76]

adjunct **post-surgical pituitary hormone replacement therapy**

Treatment recommended for SOME patients in selected patient group

Primary options

» levothyroxine: 1.8 micrograms/kg/day orally

--AND/OR--

» testosterone transdermal: 2.5 to 7.5 mg once daily, titrate according to response in men
-or-
» testosterone cipionate: 200 mg intramuscularly every 2 weeks, titrate according to response in men
-or-
» estradiol: 2 mg orally once daily in women
-or-
» conjugated oestrogens: 0.625 to 1.25 mg orally once daily in women
-and-
» medroxyprogesterone: 5-10 mg orally once daily on 10 days of each month if woman has intact uterus and on estradiol or oestrogen

--AND/OR--

» somatropin (recombinant): dose depends on brand used; consult specialist for guidance on dose

--AND/OR--

» desmopressin: 0.1 mg orally once to three times daily

» Any combination of deficiencies may occur.

» Levothyroxine is used to achieve a free T4 in the upper half of the normal range. A thyroid-stimulating hormone should not be used to guide therapy.[109]

» Testosterone therapy is used to achieve a testosterone level in the normal range.[109]

» Women with an intact uterus taking oestrogen replacement also need 10 days of progestin

Ongoing

each month in addition to oestrogen replacement therapy.

» Decision to treat with growth hormone should be individualised for each patient based on symptoms, benefits, and risk of therapy.[109] Dose titration should occur every month to achieve clinical response (i.e., energy level, sense of well-being, and lean body mass) and an insulin-like growth factor 1 (IGF-1) level in the age-adjusted mid- to upper-normal range.

» Desmopressin is titrated to control symptomatic excessive urine output. This is based on patient preference. Serum sodium and symptoms are monitored periodically to evaluate adequacy of treatment.[109]

1st **medical therapy alone**

Primary options

» osilodrostat: 2 mg orally twice daily initially, increase gradually according to response, maximum 60 mg/day

OR

» metyrapone: 0.5 to 1 g/day orally given in 3-4 divided doses initially, increase gradually according to response, maximum 6 g/day

OR

» ketoconazole: 200-600 mg/day orally given in 2-3 divided doses initially, increase gradually according to response, maximum 1600 mg/day given in 2-4 divided doses

OR

» levoketoconazole: 150 mg orally twice daily initially, increase gradually according to response, maximum 1200 mg/day

OR

» pasireotide: 0.3 to 0.9 mg subcutaneously twice daily; 10-40 mg intramuscularly every 4 weeks

OR

» cabergoline: consult specialist for guidance on dose

OR

Ongoing

» mifepristone: 300 mg orally once daily initially, increase gradually according to response, maximum 1200 mg/day

Secondary options

» mitotane: consult specialist for guidance on dose

Tertiary options

» etomidate: consult specialist for guidance on dose

» Medical treatment alone with a somatostatin analogue (pasireotide), a dopamine agonist (cabergoline), a steroidogenesis inhibitor (osilodrostat, ketoconazole, levoketoconazole, metyrapone, mitotane, and etomidate), or a glucocorticoid receptor antagonist (mifepristone) has been increasingly used in clinical practice. Medical therapy is indicated to control cortisol secretion in patients with mild hypercortisolism or where surgery is declined or not feasible (e.g., high surgical risk, metastatic disease).[88] [89] [90] [91] However, there is a paucity of high-quality studies of medical therapy in Cushing's disease, and caution should be employed when comparing efficacy rates owing to the variability in study design and quality.[91]

» Somatostatin analogue: pasireotide binds to a wide array of somatostatin receptors, with a much greater affinity for somatostatin receptor 5, which is predominantly expressed in patients with corticotroph adenomas. Use of the regular-release formulation of pasireotide decreases cortisol in most patients, but normalises cortisol levels in only 25% of patients.[92] The long-acting formulation of pasireotide normalises cortisol levels in 40% of patients.[93] It causes hyperglycaemia in most patients. This is a pituitary-targeted therapy and should be used only in patients with hypercortisolism due to ACTH-secreting pituitary tumours.[97] There is a high risk of hyperglycaemia, which requires careful patient selection, and a risk of QTc prolongation.[26]

» Dopamine agonist: cabergoline has been used off-label in the treatment of Cushing's disease in some countries.[98]

» Steroidogenesis inhibitors: osilodrostat, ketoconazole, levoketoconazole, metyrapone, mitotane, and etomidate decrease adrenal corticosteroid production.[89] [90] [99] They

Ongoing

should only be used by physicians familiar with their use. Osilodrostat is approved in the US and Europe for use in Cushing's disease. It is a potent, rapidly active steroid 11-beta-hydroxylase inhibitor and is generally well tolerated.[99] There is a risk of hypocortisolism, hypokalaemia, and QTc prolongation; careful monitoring for hyperandrogenism is needed in women.[26] Ketoconazole and metyrapone have a relatively rapid onset of steroidogenesis inhibition. Ketoconazole may cause idiopathic severe liver injury and adrenal insufficiency. Its use requires expert guidance and is contraindicated in patients with liver disease. If used, liver and adrenal function should be monitored before and during treatment.[100] [101] Levoketoconazole is an adrenal steroidogenesis inhibitor that is approved for treatment in the US.[102] [103] [104] Mitotane has slow onset of action and a narrow therapeutic window. It is rarely used for Cushing syndrome due to causes other than adrenal carcinoma. Etomidate is rarely used and is reserved for emergency situations only. It has rapid onset but must be given intravenously.[90]

» Glucocorticoid receptor antagonist: mifepristone blocks cortisol at the receptor level and attenuates the clinical and biochemical effects associated with elevation of cortisol. The US Food and Drug Administration has approved mifepristone for the treatment of hyperglycaemia associated with Cushing syndrome. It may be used for all forms of Cushing syndrome. Cortisol levels may increase during therapy with mifepristone due to feedback inhibition.[105] As such, cortisol levels should not be used to guide therapy in patients treated with mifepristone.[106]

» Patients should be monitored for development of adrenal insufficiency.

» Dose adjustment should be based on clinical symptoms, biochemical normalisation of 24-hour urinary free cortisol, and late-night salivary cortisol (with the exception of mifepristone, where use of cortisol as a marker will not be reliable).

2nd **repeat transsphenoidal pituitary adenomectomy**

» In patients who received transsphenoidal pituitary adenomectomy as first-line therapy, additional therapy should be considered in patients with failure of initial pituitary surgery or with recurrence of disease. The incidence of recurrence in Cushing's disease is high, with

Ongoing

50% of recurrences occurring during the first 50 months after first surgery.[77] Re-operation is frequently the preferred therapy if initial surgery fails. It should be considered in all patients with recurrence or persistence of disease. It is effective in about two-thirds of patients.[80] [81] [82] However, the risk of pituitary deficiency after re-operation is 50%. This is significantly higher than after initial surgical therapy.[80]

» Patients with mild cortisol excess (biochemical evidence of hypercortisolaemia but no clinical signs or symptoms of Cushing syndrome) should have therapy carefully weighed because benefit of surgery has not been convincingly demonstrated.[68]

adjunct **medical therapy before surgery**

Treatment recommended for SOME patients in selected patient group

Primary options

» osilodrostat: 2 mg orally twice daily initially, increase gradually according to response, maximum 60 mg/day

OR

» metyrapone: 0.5 to 1 g/day orally given in 3-4 divided doses initially, increase gradually according to response, maximum 6 g/day

OR

» ketoconazole: 200-600 mg/day orally given in 2-3 divided doses initially, increase gradually according to response, maximum 1600 mg/day given in 2-4 divided doses

OR

» levoketoconazole: 150 mg orally twice daily initially, increase gradually according to response, maximum 1200 mg/day

OR

» pasireotide: 0.3 to 0.9 mg subcutaneously twice daily; 10-40 mg intramuscularly every 4 weeks

OR

» cabergoline: consult specialist for guidance on dose

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OR

» mifepristone: 300 mg orally once daily initially, increase gradually according to response, maximum 1200 mg/day

Secondary options

» mitotane: consult specialist for guidance on dose

Tertiary options

» etomidate: consult specialist for guidance on dose

» A somatostatin analogue (pasireotide), a dopamine agonist (cabergoline), a steroidogenesis inhibitor (osilodrostat, ketoconazole, levoketoconazole, metyrapone, mitotane, etomidate), or a glucocorticoid receptor antagonist (mifepristone) is occasionally used for mild hypercortisolism, or short term for severe hypercortisolism, before other therapies are undertaken.[88] [89] [90] [91]

» Somatostatin analogue: pasireotide binds to a wide array of somatostatin receptors, with a much greater affinity for somatostatin receptor 5, which is predominantly expressed in corticotroph adenomas. Use of the regular-release formulation of pasireotide decreases cortisol in most patients, but normalises cortisol levels in only 25% of patients.[92] The long-acting formulation of pasireotide normalises cortisol levels in 40% of patients.[93] It causes hyperglycaemia in most patients. This is a pituitary-targeted therapy and should be used only in patients with hypercortisolism due to ACTH-secreting pituitary tumours.[97] There is a high risk of hyperglycaemia, which requires careful patient selection, and a risk of QTc prolongation.[26]

» Dopamine agonist: cabergoline has been used off-label in the treatment of Cushing's disease in some countries.[98]

» Steroidogenesis inhibitors: osilodrostat, ketoconazole, levoketoconazole, metyrapone, mitotane, and etomidate decrease adrenal corticosteroid production.[89] [90] [99] They should only be used by physicians familiar with their use. Osilodrostat is approved in the US and Europe for use in Cushing's disease. It is a potent, rapidly active steroid 11-beta-hydroxylase inhibitor and is generally well tolerated.[99] There is a risk of hypocortisolism, hypokalaemia,

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and QTc prolongation; careful monitoring for hyperandrogenism is needed in women.[26] Ketoconazole and metyrapone have a relatively rapid onset of steroidogenesis inhibition. Ketoconazole may cause idiopathic severe liver injury and adrenal insufficiency. Its use requires expert guidance and is contraindicated in patients with liver disease. If used, liver and adrenal function should be monitored before and during treatment.[100] [101] Levoketoconazole is an adrenal steroidogenesis inhibitor that is approved for treatment in the US.[102] [103] [104] Mitotane has slow onset of action and a narrow therapeutic window. It is rarely used for Cushing syndrome due to causes other than adrenal carcinoma. Etomidate is rarely used and is reserved for emergency situations only. It has rapid onset but must be given intravenously.[90]

» Glucocorticoid receptor antagonist: mifepristone blocks cortisol at the receptor level and attenuates the clinical and biochemical effects associated with elevation of cortisol. The US Food and Drug Administration has approved mifepristone for the treatment of hyperglycaemia associated with Cushing syndrome. It may be used for all forms of Cushing syndrome. Cortisol levels may increase during therapy with mifepristone due to feedback inhibition.[105] As such, cortisol levels should not be used to guide therapy in patients treated with mifepristone.[106]

» Patients should be monitored for development of adrenal insufficiency.

» Dose adjustment should be based on clinical symptoms, biochemical normalisation of 24-hour urinary free cortisol, and late-night salivary cortisol (with the exception of mifepristone, where use of cortisol as a marker will not be reliable).

adjunct **post-surgical corticosteroid replacement therapy**

Treatment recommended for SOME patients in selected patient group

Primary options

» hydrocortisone: 10-25 mg per metre square body surface area/day orally given in 2-3 divided doses; usual dose is a larger dose in the morning (10-15 mg) and a smaller dose in the late afternoon (5-10 mg)

» Patients who undergo pituitary adenomectomy may become temporarily or permanently

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dependent on physiological replacement of cortisol. It is necessary to monitor blood pressure, check for orthostatic symptoms, and assess general sense of energy or fatigue.

» As postoperative hypocortisolism is predictive of remission, some centres advocate withholding routine corticosteroid therapy after pituitary surgery and monitoring cortisol levels every 8 hours or if symptoms of adrenal insufficiency occur. If adrenal insufficiency occurs or low cortisol levels are documented, corticosteroid therapy should be initiated. Other centres begin routine corticosteroid therapy immediately after surgery and evaluate for remission of hypercortisolism later in the postoperative course.[75] This is done by measuring morning cortisol at least 24 hours after the last dose of corticosteroid therapy. Patients with a postoperative morning cortisol of <55 nanomol/L (<2 micrograms/dL) are considered to be in remission and can transition into long-term follow-up. Patients with a postoperative morning cortisol of >138 nanomol/L (>5 micrograms/dL) require further evaluation and possibly further therapy. Patients with a morning cortisol between 55 and 138 nanomol/L (2 and 5 micrograms/dL) should be followed with additional measurements to detect a drop in subsequent morning cortisol levels. Individuals with morning cortisols >55 nanomol/L (>2 micrograms/dL) after surgery are 2.5 times more likely to have recurrences than those with cortisol levels <55 nanomol/L (<2 micrograms/dL).[71] [72] [73]

» Corticosteroids are usually rapidly tapered to physiological doses within 1 week or less (often by discharge from hospital). Testing to see if the hypothalamic-pituitary-adrenal (HPA) axis has recovered can be done in follow-up by 3 months after surgery. Testing is usually a morning cortisol prior to the patient taking the morning hydrocortisone dose, if hydrocortisone therapy had been continued. Cortisol levels of >552 nanomol/L (>20 micrograms/dL) indicate recovery of the axis. Levels <83 nanomol/L (<3 micrograms/dL) indicate a continued need for corticosteroids. Levels between 83 nanomol/L (3 micrograms/dL) and 552 nanomol/L (20 micrograms/dL) should prompt further testing (cosyntropin stimulation testing, insulin tolerance testing, or metyrapone testing). Once recovery of HPA axis has been established, patients need to undergo testing for possible recurrence. Salivary cortisol testing seems to be a better predictor of early recurrence.[73] [76]

Ongoing

adjunct **post-surgical pituitary hormone replacement therapy**

Treatment recommended for SOME patients in selected patient group

Primary options

» levothyroxine: 1.8 micrograms/kg/day orally

--AND/OR--

» testosterone transdermal: 2.5 to 7.5 mg once daily, titrate according to response in men

-or-

» testosterone cipionate: 200 mg intramuscularly every 2 weeks, titrate according to response in men

-or-

» estradiol: 2 mg orally once daily in women

-or-

» conjugated oestrogens: 0.625 to 1.25 mg orally once daily in women

-and-

» medroxyprogesterone: 5-10 mg orally once daily on 10 days of each month if woman has intact uterus and on estradiol or oestrogen

--AND/OR--

» somatropin (recombinant): dose depends on brand used; consult specialist for guidance on dose

--AND/OR--

» desmopressin: 0.1 mg orally once to three times daily

» Any combination of deficiencies may occur. The risk of pituitary deficiency after reoperation is 50%. This is significantly higher than after initial surgical therapy.[80]

» Levothyroxine is used to achieve a free T4 in the upper half of the normal range. A thyroid-stimulating hormone should not be used to guide therapy.[109]

» Testosterone therapy is used to achieve a testosterone level in the normal range.[109]

» Women with an intact uterus taking oestrogen replacement also need 10 days of progestin each month in addition to oestrogen replacement therapy.

» Decision to treat with growth hormone should be individualised for each patient based on symptoms, benefits, and risk of therapy.[109] Dose titration should occur every month to achieve clinical response (i.e., energy level,

Ongoing

sense of well-being, and lean body mass) and an insulin-like growth factor 1 (IGF-1) level in the age-adjusted mid- to upper-normal range.

» Desmopressin is titrated to control symptomatic excessive urine output. This is based on patient preference. Serum sodium and symptoms are monitored periodically to evaluate adequacy of treatment.[109]

2nd **medical therapy alone**

Primary options

» osilodrostat: 2 mg orally twice daily initially, increase gradually according to response, maximum 60 mg/day

OR

» metyrapone: 0.5 to 1 g/day orally given in 3-4 divided doses initially, increase gradually according to response, maximum 6 g/day

OR

» ketoconazole: 200-600 mg/day orally given in 2-3 divided doses initially, increase gradually according to response, maximum 1600 mg/day given in 2-4 divided doses

OR

» levoketoconazole: 150 mg orally twice daily initially, increase gradually according to response, maximum 1200 mg/day

OR

» pasireotide: 0.3 to 0.9 mg subcutaneously twice daily; 10-40 mg intramuscularly every 4 weeks

OR

» cabergoline: consult specialist for guidance on dose

OR

» mifepristone: 300 mg orally once daily initially, increase gradually according to response, maximum 1200 mg/day

Secondary options

Ongoing

» mitotane: consult specialist for guidance on dose

Tertiary options

» etomidate: consult specialist for guidance on dose

» In patients who received transsphenoidal pituitary adenomectomy as first-line therapy, additional therapy should be considered in patients with failure of initial pituitary surgery or with recurrence of disease. The incidence of recurrence in Cushing's disease is high, with 50% of recurrences occurring during the first 50 months after first surgery.[77] Standard therapies include repeat pituitary surgery, radiotherapy, bilateral adrenalectomy, or medical therapy.[69] [78]

» Success rates of these treatment options vary between 25% (for some of the medical therapies) and 100% (bilateral adrenalectomy). Treatment options have specific advantages, limitations, and side-effects so treatment decisions should be individualised according to the specific needs of the patient and risk of complications.[77] [79]

» Medical treatment has been increasingly used in clinical practice and is indicated to control cortisol secretion in cases with persistent or recurrent hypercortisolism after surgery, or where surgery is declined or not feasible (e.g., high surgical risk, metastatic disease).[88] [89] [90] [91]

» Somatostatin analogue: pasireotide binds to a wide array of somatostatin receptors, with a much greater affinity for somatostatin receptor 5, which is predominantly expressed in corticotroph adenomas. Use of the regular-release formulation of pasireotide decreases cortisol in most patients, but normalises cortisol levels in only 25% of patients.[92] The long-acting formulation of pasireotide normalises cortisol levels in 40% of patients.[93] It causes hyperglycaemia in most patients. This is a pituitary-targeted therapy and should be used only in patients with hypercortisolism due to ACTH-secreting pituitary tumours.[97] There is a high risk of hyperglycaemia, which requires careful patient selection, and a risk of QTc prolongation.[26]

» Dopamine agonist: cabergoline has been used off-label in the treatment of Cushing's disease in some countries.[98]

Ongoing

» Steroidogenesis inhibitors: osilodrostat, ketoconazole, levoketoconazole, metyrapone, mitotane, and etomidate decrease adrenal corticosteroid production and can be used (though off-label in most countries) in the treatment of Cushing syndrome. They should only be used by physicians familiar with their use. Osilodrostat is approved in the US and Europe for use in Cushing's disease. It is a potent, rapidly active steroid 11-beta-hydroxylase inhibitor and is generally well tolerated.[99] There is a risk of hypocortisolism, hypokalaemia, and QTc prolongation; careful monitoring for hyperandrogenism is needed in women.[26] Ketoconazole and metyrapone have a relatively rapid onset of steroidogenesis inhibition. Ketoconazole may cause idiopathic severe liver injury and adrenal insufficiency. Its use requires expert guidance and is contraindicated in patients with liver disease. If used, liver and adrenal function should be monitored before and during treatment.[100] [101] Levoketoconazole is an adrenal steroidogenesis inhibitor that is approved for treatment in the US.[102] [103] [104] Mitotane has slow onset of action and a narrow therapeutic window. It is rarely used for Cushing syndrome due to causes other than adrenal carcinoma. Etomidate is rarely used and is reserved for emergency situations only. It has rapid onset but must be given intravenously.[90]

» Glucocorticoid receptor antagonist: mifepristone blocks cortisol at the receptor level and attenuates the clinical and biochemical effects associated with elevation of cortisol. The US Food and Drug Administration has approved mifepristone for the treatment of hyperglycaemia associated with Cushing syndrome. It may be used for all forms of Cushing syndrome. Cortisol levels may increase during therapy with mifepristone due to feedback inhibition.[105] As such, cortisol levels should not be used to guide therapy in patients treated with mifepristone.[106]

» Patients should be monitored for development of adrenal insufficiency.

» Dose adjustment should be based on clinical symptoms, biochemical normalisation of 24-hour urinary free cortisol, and late-night salivary cortisol (with the exception of mifepristone, where use of cortisol as a marker will not be reliable).

2nd **pituitary radiotherapy**

Ongoing

» Radiotherapy by conventional fractionated radiotherapy or stereotactic radiosurgery is most commonly used in patients with persistent hypercortisolism after incomplete corticotroph tumour resection, particularly if the tumour is aggressive or invasive or considered unresectable.[26] This modality is perhaps best used as part of the therapy for patients with mild residual hypercortisolism, as full effects of therapy can take several years to be realised. Radiation of tumours located close to the optic chiasm increases the risk of damage to the optic chiasm, and this risk should be considered prior to therapy.

» After 3 to 5 years, both traditional fractionated radiotherapy and stereotactic radiosurgery attain remission in 50% to 60% of patients.[83] [84] [85]

» Insufficient data exist to estimate the long-term recurrence rates after therapy.

» Traditional fractionated radiotherapy and stereotactic radiosurgery have similar rates of post-therapy hypopituitarism.

adjunct **medical therapy before radiotherapy**

Treatment recommended for SOME patients in selected patient group

Primary options

» osilodrostat: 2 mg orally twice daily initially, increase gradually according to response, maximum 60 mg/day

OR

» metyrapone: 0.5 to 1 g/day orally given in 3-4 divided doses initially, increase gradually according to response, maximum 6 g/day

OR

» ketoconazole: 200-600 mg/day orally given in 2-3 divided doses initially, increase gradually according to response, maximum 1600 mg/day given in 2-4 divided doses

OR

» levoketoconazole: 150 mg orally twice daily initially, increase gradually according to response, maximum 1200 mg/day

OR

Ongoing

» pasireotide: 0.3 to 0.9 mg subcutaneously twice daily; 10-40 mg intramuscularly every 4 weeks

OR

» cabergoline: consult specialist for guidance on dose

OR

» mifepristone: 300 mg orally once daily initially, increase gradually according to response, maximum 1200 mg/day

Secondary options

» mitotane: consult specialist for guidance on dose

Tertiary options

» etomidate: consult specialist for guidance on dose

» A somatostatin analogue (pasireotide), a dopamine agonist (cabergoline), a steroidogenesis inhibitor (osilodrostat, ketoconazole, levoketoconazole, metyrapone, mitotane, etomidate), or a glucocorticoid receptor antagonist (mifepristone) is occasionally used short term for severe hypercortisolism, before other therapies are undertaken.[88] [89] [90] [91]

» Somatostatin analogue: pasireotide binds to a wide array of somatostatin receptors, with a much greater affinity for somatostatin receptor 5, which is predominantly expressed in corticotroph adenomas. Use of the regular-release formulation of pasireotide decreases cortisol in most patients, but normalises cortisol levels in only 25% of patients.[92] The long-acting formulation of pasireotide normalises cortisol levels in 40% of patients.[93] It causes hyperglycaemia in most patients. This is a pituitary-targeted therapy and should be used only in patients with hypercortisolism due to ACTH-secreting pituitary tumours.[97] There is a high risk of hyperglycaemia, which requires careful patient selection, and a risk of QTc prolongation.[26]

» Dopamine agonist: cabergoline has been used off-label in the treatment of Cushing's disease in some countries.[98]

Ongoing

» Steroidogenesis inhibitors: osilodrostat, ketoconazole, levoketoconazole, metyrapone, mitotane, and etomidate decrease adrenal corticosteroid production.[89] [90] [99] They should only be used by physicians familiar with their use. Osilodrostat is approved in the US and Europe for use in Cushing's disease. It is a potent, rapidly active steroid 11-beta-hydroxylase inhibitor and is generally well tolerated.[99] There is a risk of hypocortisolism, hypokalaemia, and QTc prolongation; careful monitoring for hyperandrogenism is needed in women.[26] Ketoconazole and metyrapone have a relatively rapid onset of steroidogenesis inhibition. Ketoconazole may cause idiopathic severe liver injury and adrenal insufficiency. Its use requires expert guidance and is contraindicated in patients with liver disease. If used, liver and adrenal function should be monitored before and during treatment.[100] [101] Levoketoconazole is an adrenal steroidogenesis inhibitor that is approved for treatment in the US.[102] [103] [104] Mitotane has slow onset of action and a narrow therapeutic window. It is rarely used for Cushing syndrome due to causes other than adrenal carcinoma. Etomidate is rarely used and is reserved for emergency situations only. It has rapid onset but must be given intravenously.[90]

» Glucocorticoid receptor antagonist: mifepristone blocks cortisol at the receptor level and attenuates the clinical and biochemical effects associated with elevation of cortisol. The US Food and Drug Administration has approved mifepristone for the treatment of hyperglycaemia associated with Cushing syndrome. It may be used for all forms of Cushing syndrome. Cortisol levels may increase during therapy with mifepristone due to feedback inhibition.[105] As such, cortisol levels should not be used to guide therapy in patients treated with mifepristone.[106]

» Patients should be monitored for development of adrenal insufficiency.

» Dose adjustment should be based on clinical symptoms, biochemical normalisation of 24-hour urinary free cortisol, and late-night salivary cortisol (with the exception of mifepristone, where use of cortisol as a marker will not be reliable).

adjunct **post-radiation corticosteroid replacement therapy**

Treatment recommended for SOME patients in selected patient group

Ongoing

Primary options

» hydrocortisone: 10-25 mg per metre square body surface area/day orally given in 2-3 divided doses; usual dose is a larger dose in the morning (10-15 mg) and a smaller dose in the late afternoon (5-10 mg)

» Patients who undergo pituitary irradiation may become temporarily or permanently dependent on physiological replacement of cortisol. This may occur even years after therapy. Consequently, it is necessary to monitor for adrenal insufficiency for years after radiotherapy (e.g., monitor blood pressure, check for orthostatic symptoms, and assess general sense of energy or fatigue).

» Slow taper of corticosteroid replacement may be done over time if the pituitary axis recovers.

adjunct **post-radiation pituitary hormone replacement therapy**

Treatment recommended for SOME patients in selected patient group

Primary options

» levothyroxine: 1.8 micrograms/kg/day orally

--AND/OR--

» testosterone transdermal: 2.5 to 7.5 mg once daily, titrate according to response in men

-or-

» testosterone cipionate: 200 mg intramuscularly every 2 weeks, titrate according to response in men

-or-

» estradiol: 2 mg orally once daily in women

-or-

» conjugated oestrogens: 0.625 to 1.25 mg orally once daily in women

-and-

» medroxyprogesterone: 5-10 mg orally once daily on 10 days of each month if woman has intact uterus and on estradiol or oestrogen

--AND/OR--

» somatropin (recombinant): dose depends on brand used; consult specialist for guidance on dose

--AND/OR--

» desmopressin: 0.1 mg orally once to three times daily

» Any combination of deficiencies may occur.

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» Levothyroxine is used to achieve a free T4 in the upper half of the normal range. TSH should not be used to guide therapy.[109]

» Testosterone therapy is used to achieve a testosterone level in the normal range.[109]

» Women with an intact uterus taking oestrogen replacement also need 10 days of progestin each month in addition to oestrogen replacement therapy.

» Decision to treat with growth hormone should be individualised for each patient based on symptoms, benefits, and risk of therapy.[109] Dose titration should occur every month to achieve clinical response (i.e., energy level, sense of well-being, and lean body mass) and an insulin-like growth factor 1 (IGF-1) level in the age-adjusted mid- to upper-normal range.

» Desmopressin is titrated to control symptomatic excessive urine output. This is based on patient preference. Serum sodium and symptoms are monitored periodically to evaluate adequacy of treatment.[109]

2nd **bilateral adrenalectomy**

» Additional therapy should be considered in patients with failure of initial pituitary surgery or with recurrence of disease. The incidence of recurrence in Cushing's disease is high, with 50% of recurrences occurring during the first 50 months after first surgery.[77] Standard therapies include repeat pituitary surgery, radiotherapy, bilateral adrenalectomy, or medical therapy.[69] [78]

» Success rates of these treatment options vary between 25% (for some of the medical therapies) and 100% (bilateral adrenalectomy). Treatment options have specific advantages, limitations, and side-effects so treatment decisions should be individualised according to the specific needs of the patient and risk of complications.[77] [79]

» Bilateral adrenalectomy should be considered in patients with severe hypercortisolism following ineffective reoperation, or if a patient is not a candidate for reoperation, depending on patient preference and risk of complications.

» Provides cure for all endogenous hypercortisolism. A meta-analysis of 37 studies (1320 patients, 82% with Cushing's disease, 13% with ectopic Cushing syndrome, and 5% with primary adrenal hyperplasia) showed

Ongoing

that bilateral adrenalectomy is relatively safe and provides adequate success.[108] Although residual cortisol secretion due to accessory adrenal tissue or adrenal remnants was found in 3% to 34%, less than 2% had a relapse of Cushing syndrome. Symptoms of hypercortisolism (e.g., hypertension, obesity, or depression) improved in the majority of the patients after bilateral adrenalectomy (7 studies, 195 patients).

» Creates adrenal insufficiency with the need for lifelong corticosteroid replacement.

» Increases the risk of Nelson syndrome, which is progression of the ACTH-secreting pituitary adenoma. This progression can cause hyperpigmentation from excessive ACTH and intracranial compressive symptoms from growth of the tumour outside the sella.

» Newer laparoscopic methods of adrenalectomy allow for more rapid recovery and tolerability.

plus **permanent post-surgical corticosteroid and mineralocorticoid replacement therapy**

Treatment recommended for ALL patients in selected patient group

Primary options

» hydrocortisone: 10-25 mg per metre square body surface area/day orally given in 2-3 divided doses; usual dose is a larger dose in the morning (10-15 mg) and a smaller dose in the late afternoon (5-10 mg)
-and-
» fludrocortisone: 0.05 to 0.1 mg orally once daily

» It is necessary to monitor blood pressure, check for orthostatic symptoms, and assess general sense of energy or fatigue at regular intervals.

» Replacement glucocorticoids and mineralocorticoids are necessary in patients who undergo bilateral adrenalectomy.

adjunct **medical therapy before surgery**

Treatment recommended for SOME patients in selected patient group

Primary options

» osilodrostat: 2 mg orally twice daily initially, increase gradually according to response, maximum 60 mg/day

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OR

» metyrapone: 0.5 to 1 g/day orally given in 3-4 divided doses initially, increase gradually according to response, maximum 6 g/day

OR

» ketoconazole: 200-600 mg/day orally given in 2-3 divided doses initially, increase gradually according to response, maximum 1600 mg/day given in 2-4 divided doses

OR

» levoketoconazole: 150 mg orally twice daily initially, increase gradually according to response, maximum 1200 mg/day

OR

» pasireotide: 0.3 to 0.9 mg subcutaneously twice daily; 10-40 mg intramuscularly every 4 weeks

OR

» cabergoline: consult specialist for guidance on dose

OR

» mifepristone: 300 mg orally once daily initially, increase gradually according to response, maximum 1200 mg/day

Secondary options

» mitotane: consult specialist for guidance on dose

Tertiary options

» etomidate: consult specialist for guidance on dose

» A somatostatin analogue (pasireotide), a dopamine agonist (cabergoline), a steroidogenesis inhibitor (osilodrostat, ketoconazole, levoketoconazole, metyrapone, mitotane, etomidate), or a glucocorticoid receptor antagonist (mifepristone) is occasionally used short term for severe hypercortisolism, before other therapies are undertaken.[88] [89] [90] [91]

Ongoing

» Somatostatin analogue: pasireotide binds to a wide array of somatostatin receptors, with a much greater affinity for somatostatin receptor 5, which is predominantly expressed in corticotroph adenomas. Use of the regular-release formulation of pasireotide decreases cortisol in most patients, but normalises cortisol levels in only 25% of patients.[92] The long-acting formulation of pasireotide normalises cortisol levels in 40% of patients.[93] It causes hyperglycaemia in most patients. This is a pituitary-targeted therapy and should be used only in patients with hypercortisolism due to ACTH-secreting pituitary tumours.[97] There is a high risk of hyperglycaemia, which requires careful patient selection, and a risk of QTc prolongation.[26]

» Dopamine agonist: cabergoline has been used off-label in the treatment of Cushing's disease in some countries.[98]

» Steroidogenesis inhibitors: osilodrostat, ketoconazole, levoketoconazole, metyrapone, mitotane, and etomidate decrease adrenal corticosteroid production.[89] [90] [99] They should only be used by physicians familiar with their use. Osilodrostat is approved in the US and Europe for use in Cushing's disease. It is a potent, rapidly active steroid 11-beta-hydroxylase inhibitor and is generally well tolerated.[99] There is a risk of hypocortisolism, hypokalaemia, and QTc prolongation; careful monitoring for hyperandrogenism is needed in women.[26] Ketoconazole and metyrapone have a relatively rapid onset of steroidogenesis inhibition. Ketoconazole may cause idiopathic severe liver injury and adrenal insufficiency. Its use requires expert guidance and is contraindicated in patients with liver disease. If used, liver and adrenal function should be monitored before and during treatment.[100] [101] Levoketoconazole is an adrenal steroidogenesis inhibitor that is approved for treatment in the US.[102] [103] [104] Mitotane has slow onset of action and a narrow therapeutic window. It is rarely used for Cushing syndrome due to causes other than adrenal carcinoma. Etomidate is rarely used and is reserved for emergency situations only. It has rapid onset but must be given intravenously.[90]

» Glucocorticoid receptor antagonist: mifepristone blocks cortisol at the receptor level and attenuates the clinical and biochemical effects associated with elevation of cortisol. The US Food and Drug Administration has approved mifepristone for the treatment of

Ongoing

hyperglycaemia associated with Cushing syndrome. It may be used for all forms of Cushing syndrome. Cortisol levels may increase during therapy with mifepristone due to feedback inhibition.[105] As such, cortisol levels should not be used to guide therapy in patients treated with mifepristone.[106]

» Patients should be monitored for development of adrenal insufficiency.

» Dose adjustment should be based on clinical symptoms, biochemical normalisation of 24-hour urinary free cortisol, and late-night salivary cortisol (with the exception of mifepristone, where use of cortisol as a marker will not be reliable).

ectopic ACTH or corticotrophin-releasing hormone (CRH) syndrome

1st **surgical resection or ablation of tumour and metastases**

» Resection or ablation of ectopic tumours producing ACTH or CRH is the preferred mode of therapy. Many cases have severe hypercortisolism requiring steroidogenesis inhibition therapy in addition to surgery.

adjunct **medical therapy before surgery**

Treatment recommended for SOME patients in selected patient group

Primary options

» osilodrostat: 2 mg orally twice daily initially, increase gradually according to response, maximum 60 mg/day

OR

» mifepristone: 300 mg orally once daily initially, increase gradually according to response, maximum 1200 mg/day

OR

» ketoconazole: 200-600 mg/day orally given in 2-3 divided doses initially, increase gradually according to response, maximum 1600 mg/day given in 2-4 divided doses

OR

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» levoketoconazole: 150 mg orally twice daily initially, increase gradually according to response, maximum 1200 mg/day

OR

» metyrapone: 0.5 to 1 g/day orally given in 3-4 divided doses initially, increase gradually according to response, maximum 6 g/day

Secondary options

» mitotane: consult specialist for guidance on dose

Tertiary options

» etomidate: consult specialist for guidance on dose

» Patients with ectopic ACTH-producing tumours may have extremely severe hypercortisolism, and require reduction in cortisol before proceeding to surgery. In these cases, steroidogenesis inhibitor therapy (ketoconazole, levoketoconazole, metyrapone, osilodrostat, mitotane, etomidate) or a glucocorticoid receptor antagonist (mifepristone) can be used to block cortisol action or lower cortisol levels in preparation before surgery.[90]

» These agents should only be used by physicians familiar with their use. Osilodrostat is a potent oral inhibitor of steroidogenesis (inhibits steroid 11-beta-hydroxylase) that is approved in the US for the treatment of Cushing's disease in patients where pituitary surgery is not an option or has not been curative, and in Europe and Japan for the treatment of endogenous Cushing syndrome.[26] [99] Ketoconazole and metyrapone have a relatively rapid onset of steroidogenesis inhibition. Ketoconazole may cause idiopathic severe liver injury and adrenal insufficiency. Its use requires expert guidance and is contraindicated in patients with liver disease. If used, liver and adrenal function should be monitored before and during treatment.[100] [101] Levoketoconazole is an adrenal steroidogenesis inhibitor that is approved for treatment in the US.[102] [103] [104] Mitotane has slow onset of action and a narrow therapeutic window. It is rarely used for Cushing syndrome due to causes other than adrenal carcinoma. Etomidate is rarely used and is reserved for emergency situations only. It has rapid onset but must be given intravenously.[90]

Ongoing

» Mifepristone blocks cortisol at the receptor level and attenuates the clinical and biochemical effects associated with elevation of cortisol. The US Food and Drug Administration has approved mifepristone for the treatment of hyperglycaemia associated with Cushing syndrome. It may be used for all forms of Cushing syndrome. Cortisol levels may increase during therapy with mifepristone due to feedback inhibition.[105] As such, cortisol levels should not be used to guide therapy in patients treated with mifepristone.[106]

» Patients should be monitored for development of adrenal insufficiency.

» Dose adjustment should be based on clinical symptoms, biochemical normalisation of 24-hour urinary free cortisol, and late-night salivary cortisol (with the exception of mifepristone, where use of cortisol as a marker will not be reliable).

adjunct **chemotherapy or radiotherapy for primary tumour**

Treatment recommended for SOME patients in selected patient group

» Depending upon the tumour source of the ectopic ACTH or CRH syndrome, adjunctive chemotherapy and/or radiotherapy may be indicated.

» See local specialist protocol for dosing guidelines.

2nd **bilateral adrenalectomy**

» Should be considered if surgical resection is not possible, depending on patient preference and risk of complications.

» Provides cure for all endogenous hypercortisolism.

» Creates adrenal insufficiency with the need for lifelong corticosteroid replacement.

plus **permanent post-surgical corticosteroid and mineralocorticoid replacement therapy**

Treatment recommended for ALL patients in selected patient group

Primary options

» hydrocortisone: 10-25 mg per metre square body surface area/day orally given in 2-3 divided doses; usual dose is a larger dose in

Ongoing

the morning (10-15 mg) and a smaller dose in the late afternoon (5-10 mg)
-and-
» fludrocortisone: 0.05 to 0.1 mg orally once daily

» It is necessary to monitor blood pressure, check for orthostatic symptoms, and assess general sense of energy or fatigue.

» Replacement glucocorticoids and mineralocorticoids are necessary in patients who undergo bilateral adrenalectomy.

adjunct **medical therapy before surgery**

Treatment recommended for SOME patients in selected patient group

Primary options

» osilodrostat: 2 mg orally twice daily initially, increase gradually according to response, maximum 60 mg/day

OR

» mifepristone: 300 mg orally once daily initially, increase gradually according to response, maximum 1200 mg/day

OR

» ketoconazole: 200-600 mg/day orally given in 2-3 divided doses initially, increase gradually according to response, maximum 1600 mg/day given in 2-4 divided doses

OR

» levoketoconazole: 150 mg orally twice daily initially, increase gradually according to response, maximum 1200 mg/day

OR

» metyrapone: 0.5 to 1 g/day orally given in 3-4 divided doses initially, increase gradually according to response, maximum 6 g/day

Secondary options

» mitotane: consult specialist for guidance on dose

Tertiary options

Ongoing

» etomidate: consult specialist for guidance on dose

» Patients with ectopic ACTH-producing tumours may have extremely severe hypercortisolism, and require reduction in cortisol before proceeding to surgery. In these cases, steroidogenesis inhibitor therapy (ketoconazole, levoketoconazole, metyrapone, osilodrostat, mitotane, etomidate) or a glucocorticoid receptor antagonist (mifepristone) can be used to block cortisol action or lower cortisol levels in preparation before surgery.[90]

» These agents should only be used by physicians familiar with their use. Osilodrostat is a potent oral inhibitor of steroidogenesis (inhibits steroid 11-beta-hydroxylase) that is approved in the US for the treatment of Cushing's disease in patients where pituitary surgery is not an option or has not been curative, and in Europe and Japan for the treatment of endogenous Cushing syndrome.[26] [99] Ketoconazole and metyrapone have a relatively rapid onset of steroidogenesis inhibition. Ketoconazole may cause idiopathic severe liver injury and adrenal insufficiency. Its use requires expert guidance and is contraindicated in patients with liver disease. If used, liver and adrenal function should be monitored before and during treatment.[100] [101] Levoketoconazole is an adrenal steroidogenesis inhibitor that is approved for treatment in the US.[102] [103] [104] Mitotane has slow onset of action and a narrow therapeutic window. It is rarely used for Cushing syndrome due to causes other than adrenal carcinoma. Etomidate is rarely used and is reserved for emergency situations only. It has rapid onset but must be given intravenously.[90]

» Mifepristone blocks cortisol at the receptor level and attenuates the clinical and biochemical effects associated with elevation of cortisol. The US Food and Drug Administration has approved mifepristone for the treatment of hyperglycaemia associated with Cushing syndrome. It may be used for all forms of Cushing syndrome. Cortisol levels may increase during therapy with mifepristone due to feedback inhibition.[105] As such, cortisol levels should not be used to guide therapy in patients treated with mifepristone.[106]

» Patients should be monitored for development of adrenal insufficiency.

» Dose adjustment should be based on clinical symptoms, biochemical normalisation of 24-

Ongoing

hour urinary free cortisol, and late-night salivary cortisol (with the exception of mifepristone, where use of cortisol as a marker will not be reliable).

adjunct **chemotherapy or radiotherapy for primary tumour**

Treatment recommended for SOME patients in selected patient group

» Depending upon the tumour source of the ectopic ACTH or CRH syndrome, adjunctive chemotherapy and/or radiotherapy may be indicated.

» See local specialist protocol for dosing guidelines.

3rd **medical therapy only**

Primary options

» osilodrostat: 2 mg orally twice daily initially, increase gradually according to response, maximum 60 mg/day

OR

» mifepristone: 300 mg orally once daily initially, increase gradually according to response, maximum 1200 mg/day

OR

» ketoconazole: 200-600 mg/day orally given in 2-3 divided doses initially, increase gradually according to response, maximum 1600 mg/day given in 2-4 divided doses

OR

» levoketoconazole: 150 mg orally twice daily initially, increase gradually according to response, maximum 1200 mg/day

OR

» metyrapone: 0.5 to 1 g/day orally given in 3-4 divided doses initially, increase gradually according to response, maximum 6 g/day

Secondary options

» mitotane: consult specialist for guidance on dose

Tertiary options

MANAGEMENT

Ongoing

» etomidate: consult specialist for guidance on dose

» There is a paucity of high-quality studies of medical therapy in Cushing syndrome.[91] The decision about which therapy to use should be individualised for each patient, factoring patient preference and risk of complications into any decision.[90]

» Steroidogenesis inhibitors: ketoconazole, levoketoconazole, metyrapone, osilodrostat, mitotane, and etomidate decrease adrenal corticosteroid production and can be used (though off-label in most countries) in the treatment of Cushing syndrome.[90] These agents should only be used by physicians familiar with their use. Osilodrostat is a potent oral inhibitor of steroidogenesis (inhibits steroid 11-beta-hydroxylase) that is approved in the US for the treatment of Cushing's disease in patients where pituitary surgery is not an option or has not been curative, and in Europe and Japan for the treatment of endogenous Cushing syndrome.[26] [99] Ketoconazole and metyrapone have a relatively rapid onset of steroidogenesis inhibition. Ketoconazole may cause idiopathic severe liver injury and adrenal insufficiency. Its use requires expert guidance and is contraindicated in patients with liver disease. If used, liver and adrenal function should be monitored before and during treatment.[101] Levoketoconazole is an adrenal steroidogenesis inhibitor that is approved for treatment in the US.[102] [103] [104] Mitotane has slow onset of action and a narrow therapeutic window. It is rarely used for Cushing syndrome due to causes other than adrenal carcinoma. Etomidate is rarely used and is reserved for emergency situations only. It has rapid onset but must be given intravenously.[90]

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Ongoing

» Patients should be monitored for development of adrenal insufficiency.

» Dose adjustment should be based on clinical symptoms, biochemical normalisation of 24-hour urinary free cortisol, and late-night salivary cortisol (with the exception of mifepristone, where use of cortisol as a marker will not be reliable).

adjunct **chemotherapy or radiotherapy for primary tumour**

Treatment recommended for SOME patients in selected patient group

» Depending upon the tumour source of the ectopic ACTH or CRH syndrome, adjunctive chemotherapy and/or radiotherapy may be indicated.

» See local specialist protocol for dosing guidelines.

ACTH-independent due to unilateral adrenal carcinoma or adenoma

1st **unilateral adrenalectomy or tumour resection**

» Preferred method of therapy in patients with unilateral cortisol-secreting adrenal adenoma. Laparoscopic adrenalectomy is the preferred method in most cases. Complete resection of the adrenal gland cures hypercortisolism in all patients without high risk of long-term adrenal insufficiency. Adrenalectomy has a beneficial effect on cardiovascular risk factors in patients with subclinical Cushing syndrome overall and compared with conservative management.[110]

» Patients with mild cortisol excess (biochemical evidence of hypercortisolaemia but no clinical signs or symptoms of Cushing syndrome) should have therapy carefully weighed because benefit of surgery has not been demonstrated.[51] [52]

» Adrenal carcinoma is extremely rare. First-line therapy in many patients is surgical resection of the tumour; however, at the time of diagnosis the disease has often progressed beyond the point where surgical therapy is effective. The effectiveness of chemotherapy and adjunctive therapies in both early- and late-stage disease has shown mixed results in clinical trials; however, patients should be considered for treatment with mitotane and enrolment in clinical trials (if available).[10]

adjunct **medical therapy before surgery**

Ongoing

Treatment recommended for SOME patients in selected patient group

Primary options

» osilodrostat: 2 mg orally twice daily initially, increase gradually according to response, maximum 60 mg/day

OR

» mifepristone: 300 mg orally once daily initially, increase gradually according to response, maximum 1200 mg/day

OR

» ketoconazole: 200-600 mg/day orally given in 2-3 divided doses initially, increase gradually according to response, maximum 1600 mg/day given in 2-4 divided doses

OR

» levoketoconazole: 150 mg orally twice daily initially, increase gradually according to response, maximum 1200 mg/day

OR

» metyrapone: 0.5 to 1 g/day orally given in 3-4 divided doses initially, increase gradually according to response, maximum 6 g/day

OR

» mitotane: consult specialist for guidance on dose

Secondary options

» etomidate: consult specialist for guidance on dose

» Steroidogenesis inhibitors: ketoconazole, levoketoconazole, metyrapone, osilodrostat, mitotane, and etomidate decrease adrenal corticosteroid production. They are generally used short term for severe hypercortisolism, before other therapies are undertaken.[90] These agents should only be used by physicians familiar with their use. Osilodrostat is a potent oral inhibitor of steroidogenesis (inhibits steroid 11-beta-hydroxylase) that is approved in the US for the treatment of Cushing's disease in patients where pituitary surgery is not an

Ongoing

option or has not been curative, and in Europe and Japan for the treatment of endogenous Cushing syndrome.[26] [99] Ketoconazole and metyrapone have a relatively rapid onset of steroidogenesis inhibition. Ketoconazole may cause idiopathic severe liver injury and adrenal insufficiency. Its use requires expert guidance and is contraindicated in patients with liver disease. If used, liver and adrenal function should be monitored before and during treatment.[100] [101] Levoketoconazole is an adrenal steroidogenesis inhibitor that is approved for treatment in the US.[102] [103] [104] Mitotane has slow onset of action and a narrow therapeutic window. It is rarely used for Cushing syndrome due to causes other than adrenal carcinoma. Etomidate is rarely used and is reserved for emergency situations only. It has rapid onset but must be given intravenously.[90]

» Glucocorticoid receptor antagonist: mifepristone blocks cortisol at the receptor level and attenuates the clinical and biochemical effects associated with elevation of cortisol. The US Food and Drug Administration has approved mifepristone for the treatment of hyperglycaemia associated with Cushing syndrome. It may be used for all forms of Cushing syndrome. Cortisol levels may increase during therapy with mifepristone due to feedback inhibition.[105] As such, cortisol levels should not be used to guide therapy in patients treated with mifepristone.[106]

» Patients should be monitored for development of adrenal insufficiency.

» Dose adjustment should be based on clinical symptoms, biochemical normalisation of 24-hour urinary free cortisol, and late-night salivary cortisol (with the exception of mifepristone, where use of cortisol as a marker will not be reliable).

adjunct **chemotherapy or radiotherapy for adrenal carcinoma**

Treatment recommended for SOME patients in selected patient group

» Depending upon the stage of adrenal carcinoma, adjunctive chemotherapy and/or radiotherapy may be indicated.

» See local specialist protocol for dosing guidelines.

2nd **medical therapy only**

Primary options

MANAGEMENT

Ongoing

» osilodrostat: 2 mg orally twice daily initially, increase gradually according to response, maximum 60 mg/day

OR

» mifepristone: 300 mg orally once daily initially, increase gradually according to response, maximum 1200 mg/day

OR

» ketoconazole: 200-600 mg/day orally given in 2-3 divided doses initially, increase gradually according to response, maximum 1600 mg/day given in 2-4 divided doses

OR

» levoketoconazole: 150 mg orally twice daily initially, increase gradually according to response, maximum 1200 mg/day

OR

» metyrapone: 0.5 to 1 g/day orally given in 3-4 divided doses initially, increase gradually according to response, maximum 6 g/day

OR

» mitotane: consult specialist for guidance on dose

Secondary options

» etomidate: consult specialist for guidance on dose

» Steroidogenesis inhibitors: osilodrostat, ketoconazole, levoketoconazole, metyrapone, mitotane, and etomidate decrease adrenal corticosteroid production and can be used (though off-label in most countries) in the treatment of Cushing syndrome.[90] These agents should only be used by physicians familiar with their use. Osilodrostat is a potent oral inhibitor of steroidogenesis (inhibits steroid 11-beta-hydroxylase) that is approved in the US for the treatment of Cushing's disease in patients where pituitary surgery is not an option or has not been curative, and in Europe and Japan for the treatment of endogenous Cushing syndrome.[26] [99] Ketoconazole and metyrapone have a relatively rapid onset of steroidogenesis inhibition. Ketoconazole

Ongoing

		may cause idiopathic severe liver injury and adrenal insufficiency. Its use requires expert guidance and is contraindicated in patients with liver disease. If used, liver and adrenal function should be monitored before and during treatment.[100] [101] Levoketoconazole is an adrenal steroidogenesis inhibitor that is approved for treatment in the US.[102] [103] [104] Mitotane has slow onset of action and a narrow therapeutic window. It is rarely used for Cushing syndrome due to causes other than adrenal carcinoma. Etomidate is rarely used and is reserved for emergency situations only. It has rapid onset but must be given intravenously.[90] » Glucocorticoid receptor antagonist: mifepristone blocks cortisol at the receptor level and attenuates the clinical and biochemical effects associated with elevation of cortisol. The US Food and Drug Administration has approved mifepristone for the treatment of hyperglycaemia associated with Cushing syndrome. It may be used for all forms of Cushing syndrome. Cortisol levels may increase during therapy with mifepristone due to feedback inhibition.[105] As such, cortisol levels should not be used to guide therapy in patients treated with mifepristone.[106] » Patients should be monitored for development of adrenal insufficiency. » Dose adjustment should be based on clinical symptoms, biochemical normalisation of 24-hour urinary free cortisol, and late-night salivary cortisol (with the exception of mifepristone, where use of cortisol as a marker will not be reliable).
	adjunct	**chemotherapy or radiotherapy for adrenal carcinoma** Treatment recommended for SOME patients in selected patient group » Depending upon the stage of adrenal carcinoma, adjunctive chemotherapy and/or radiotherapy may be indicated. » See local specialist protocol for dosing guidelines.
ACTH-independent due to bilateral adrenal disease (hyperplasia or adenoma)		
	1st	**bilateral adrenalectomy**

MANAGEMENT

Ongoing

» First-line therapy in patients with bilateral adrenal disease from autonomous nodule formation or bilateral hyperplasia.

» Provides cure for all endogenous hypercortisolism. Creates adrenal insufficiency with the need for lifelong corticosteroid replacement.

plus **permanent post-surgical corticosteroid and mineralocorticoid replacement therapy**

Treatment recommended for ALL patients in selected patient group

Primary options

» hydrocortisone: 10-25 mg per metre square body surface area/day orally given in 2-3 divided doses; usual dose is a larger dose in the morning (10-15 mg) and a smaller dose in the late afternoon (5-10 mg)
-and-
» fludrocortisone: 0.05 to 0.1 mg orally once daily

» It is necessary to monitor blood pressure, check for orthostatic symptoms, and assess general sense of energy or fatigue.

» Replacement glucocorticoids and mineralocorticoids are necessary in patients who undergo bilateral adrenalectomy.

adjunct **medical therapy before surgery**

Treatment recommended for SOME patients in selected patient group

Primary options

» osilodrostat: 2 mg orally twice daily initially, increase gradually according to response, maximum 60 mg/day

OR

» mifepristone: 300 mg orally once daily initially, increase gradually according to response, maximum 1200 mg/day

OR

» ketoconazole: 200-600 mg/day orally given in 2-3 divided doses initially, increase gradually according to response, maximum 1600 mg/day given in 2-4 divided doses

OR

Ongoing

» levoketoconazole: 150 mg orally twice daily initially, increase gradually according to response, maximum 1200 mg/day

OR

» metyrapone: 0.5 to 1 g/day orally given in 3-4 divided doses initially, increase gradually according to response, maximum 6 g/day

Secondary options

» mitotane: consult specialist for guidance on dose

Tertiary options

» etomidate: consult specialist for guidance on dose

» Steroidogenesis inhibitors: osilodrostat, ketoconazole, levoketoconazole, metyrapone, mitotane, and etomidate decrease adrenal corticosteroid production. They are generally used short term for severe hypercortisolism, before other therapies are undertaken.[90] These agents should only be used by physicians familiar with their use. Osilodrostat is a potent oral inhibitor of steroidogenesis (inhibits steroid 11-beta-hydroxylase) that is approved in the US for the treatment of Cushing's disease in patients where pituitary surgery is not an option or has not been curative, and in Europe and Japan for the treatment of endogenous Cushing syndrome.[26] [99] Ketoconazole and metyrapone have a relatively rapid onset of steroidogenesis inhibition. Ketoconazole may cause idiopathic severe liver injury and adrenal insufficiency. Its use requires expert guidance and is contraindicated in patients with liver disease. If used, liver and adrenal function should be monitored before and during treatment.[100] [101] Levoketoconazole is an adrenal steroidogenesis inhibitor that is approved for treatment in the US.[102] [103] [104] Mitotane has slow onset of action and a narrow therapeutic window. It is rarely used for Cushing syndrome due to causes other than adrenal carcinoma. Etomidate is rarely used and is reserved for emergency situations only. It has rapid onset but must be given intravenously.[69]

» Glucocorticoid receptor antagonist: mifepristone blocks cortisol at the receptor level and attenuates the clinical and biochemical effects associated with elevation of cortisol.

Ongoing

The US Food and Drug Administration has approved mifepristone for the treatment of hyperglycaemia associated with Cushing syndrome. It may be used for all forms of Cushing syndrome. Cortisol levels may increase during therapy with mifepristone due to feedback inhibition.[105] As such, cortisol levels should not be used to guide therapy in patients treated with mifepristone.[106]

» Patients should be monitored for development of adrenal insufficiency.

» Dose adjustment should be based on clinical symptoms, biochemical normalisation of 24-hour urinary free cortisol, and late-night salivary cortisol (with the exception of mifepristone, where use of cortisol as a marker will not be reliable).

2nd **medical therapy only**

Primary options

» osilodrostat: 2 mg orally twice daily initially, increase gradually according to response, maximum 60 mg/day

OR

» mifepristone: 300 mg orally once daily initially, increase gradually according to response, maximum 1200 mg/day

OR

» ketoconazole: 200-600 mg/day orally given in 2-3 divided doses initially, increase gradually according to response, maximum 1600 mg/day given in 2-4 divided doses

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» levoketoconazole: 150 mg orally twice daily initially, increase gradually according to response, maximum 1200 mg/day

OR

» metyrapone: 0.5 to 1 g/day orally given in 3-4 divided doses initially, increase gradually according to response, maximum 6 g/day

Secondary options

» mitotane: consult specialist for guidance on dose

Ongoing

Tertiary options

» etomidate: consult specialist for guidance on dose

» Steroidogenesis inhibitors: osilodrostat, ketoconazole, levoketoconazole, metyrapone, mitotane, and etomidate decrease adrenal corticosteroid production and can be used (though off-label in most countries) in the treatment of Cushing syndrome.[90] These agents should only be used by physicians familiar with their use. Osilodrostat is a potent oral inhibitor of steroidogenesis (inhibits steroid 11-beta-hydroxylase) that is approved in the US for the treatment of Cushing's disease in patients where pituitary surgery is not an option or has not been curative, and in Europe and Japan for the treatment of endogenous Cushing syndrome.[26] [99] Ketoconazole and metyrapone have a relatively rapid onset of steroidogenesis inhibition. Ketoconazole may cause idiopathic severe liver injury and adrenal insufficiency. Its use requires expert guidance and is contraindicated in patients with liver disease. If used, liver and adrenal function should be monitored before and during treatment.[101] Levoketoconazole is an adrenal steroidogenesis inhibitor that is approved for treatment in the US.[102] [103] [104] Mitotane has slow onset of action and a narrow therapeutic window. It is rarely used for Cushing syndrome due to causes other than adrenal carcinoma. Etomidate is rarely used and is reserved for emergency situations only. It has rapid onset but must be given intravenously.[90]

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» Patients should be monitored for development of adrenal insufficiency.

» Dose adjustment should be based on clinical symptoms, biochemical normalisation of 24-

Ongoing

hour urinary free cortisol, and late-night salivary cortisol (with the exception of mifepristone, where use of cortisol as a marker will not be reliable).

Secondary prevention

Exogenous Cushing syndrome may be prevented in patients who require exogenous corticosteroid treatment, by reducing corticosteroid use to an absolute minimum required dose and frequency whenever possible.

Standard cardiovascular screening and treatment should be applied to patients with Cushing syndrome.

Patient discussions

Care should be taken to control complications such as diabetes, hypertension, and dyslipidaemia. Patients should be advised that adherence to medical management of these conditions can improve quality of life and life expectancy.

FOLLOW UP

Monitoring

Monitoring

Recurrence of adrenocorticotrophic hormone-dependent Cushing syndrome is common, with at least a 5% to 26% risk of recurrence at 5 years. Screen patients who have achieved remission after hypothalamic-pituitary-adrenal (HPA) axis recovery for recurrence of disease and then annually or sooner if there is clinical suspicion.[26] Use one of four high-sensitivity tests (late-night salivary cortisol, 1 mg overnight dexamethasone suppression testing, 24-hour urinary free cortisol, or desmopressin testing) to detect recurrence. Late-night salivary cortisol is the most sensitive test for detecting recurrence and should be done annually after HPA axis recovery postoperatively and then annually.[26]

Many patients are supported with corticosteroids following pituitary surgery but should be assessed for remission during the first postoperative week.[68] This is most easily done by measurement of the morning cortisol at least 24 hours after the last dose of corticosteroid therapy. Patients with a postoperative morning cortisol of <55 nanomol/L (<2 micrograms/dL) are considered to be in remission and can transition into long-term follow-up. Patients with a postoperative morning cortisol of >138 nanomol/L (>5 micrograms/dL) require further evaluation and possibly further therapy. Patients with a morning cortisol between 55 and 138 nanomol/L (2 and 5 micrograms/dL) should be followed with additional morning measurements to detect a drop in subsequent cortisol levels. Individuals with morning cortisols >55 nanomol/L (>2 micrograms/dL) after surgery are 2.5 times more likely to have recurrences than those with cortisol levels <55 nanomol/L (<2 micrograms/dL).[72]

As postoperative hypocortisolism is predictive of remission, some centres advocate withholding routine corticosteroid therapy after pituitary surgery and monitoring cortisol levels every 8 hours or if symptoms of adrenal insufficiency occur.[74] If adrenal insufficiency occurs or low cortisol levels are documented, corticosteroid therapy should be initiated. Other centres begin routine corticosteroid therapy immediately after surgery and evaluate for remission of hypercortisolism later in the postoperative course. Corticosteroids are usually rapidly tapered to physiological doses within 1 week or less (often by discharge from hospital). Testing to see if the hypothalamic-pituitary-adrenal axis has recovered can be done in follow-up by 3 months after surgery. Testing is usually a morning cortisol prior to the patient taking the morning hydrocortisone dose, if continued. Cortisol levels of >552 nanomol/L (>20 micrograms/dL) indicate recovery of the axis. Levels <83 nanomol/L (<3 micrograms/dL) indicate continued need for corticosteroids. Levels between 83 nanomol/L (3 micrograms/dL) and 552 nanomol/L (20 micrograms/dL) should prompt further testing (cosyntropin stimulation testing, insulin tolerance testing, or metyrapone testing).

Standard testing, follow-up, and management for associated conditions of hypertension, diabetes, and osteoporosis should be undertaken, as these conditions may persist after effective treatment of hypercortisolism.

Complications

Complications	Timeframe	Likelihood
adrenal insufficiency secondary to adrenal suppression	**short term**	**high**
This may occur following surgery. Pathological hypercortisolism can lead to suppression of the normal hypothalamic-pituitary-adrenal (HPA) axis. Following treatment, the normal function of the HPA axis often remains suppressed for several months. The resultant adrenal insufficiency necessitates treatment with glucocorticoid therapy until the HPA axis recovers normal function.		
cardiovascular disease	**long term**	**high**
The major cause of mortality in patients with Cushing syndrome.[113] It is difficult to tell if the increase in cardiovascular mortality is due to the development of traditional risk factors such as hypertension, diabetes, and dyslipidaemia, or to hypercortisolism itself.[121] Risk factor modification and resolution of hypercortisolism are the keys to lowering cardiovascular mortality. Standard cardiovascular screening and treatment should be applied to patients with Cushing syndrome. Adrenalectomy has a beneficial effect on cardiovascular risk factors in patients with subclinical Cushing syndrome overall and compared with conservative management.[110]		
hypertension	**long term**	**high**
Occurs in 70% to 80% of patients.[122] Occurs equally in adrenocorticotrophic hormone-dependent and -independent Cushing syndrome. Generally mild to moderate but can be severe. Blood pressure usually normalises after successful therapy, but can persist secondary to vascular remodelling. No specific class of antihypertensive agent has been shown to have increased efficacy; standard agents for therapy of hypertension should be used.		
diabetes mellitus	**long term**	**high**
Occurs in 20% to 60% of patients.[122] Glycaemic control can be very difficult in patients with hypercortisolism. No agent or combination of agents has been shown to be more effective in patients with Cushing syndrome than in other patients with diabetes. Insulin is often needed to adequately control blood sugars.		
hypercoagulability	**long term**	**high**
Alterations in haemostatic parameters and in vivo endothelial dysfunction lead to increased thrombotic events.[26] [123] Prophylactic anticoagulation should be considered for patients at risk for venous thromboembolism, including: history of embolism or abnormal coagulation testing; severe preoperative hypercortisolism; current use of oestrogen or oral contraceptives; poor mobility; extended preoperative or postoperative hospital stay; and high postoperative cortisol levels or cortisol over-replacement in patients with adrenal insufficiency.[26]		
osteoporosis	**long term**	**medium**
Premature osteoporosis and fracture are seen in around 50% of patients.[56] Excessive bone exposure to glucocorticoids causes decreased osteoblast activity, and also increases osteoclast activity. It may also interfere with calcium absorption in the gastrointestinal tract, further worsening bone disease. Patients		

FOLLOW UP

Complications	Timeframe	Likelihood
should have periodic bone density assessments. Patients with persistent hypercortisolism and low or falling bone density should be treated with bisphosphonates.		
nephrolithiasis	**long term**	**medium**
Calcium renal stones occur in some patients.[23] The aetiology is related to altered calcium handling by the kidney in patients with cortisol excess. The most effective therapy is treatment of hypercortisolism. Therapies used for other patients with nephrolithiasis should also be employed.		
Nelson syndrome after bilateral adrenalectomy	**long term**	**low**
Progression of a pituitary adenoma after bilateral adrenalectomy can result in intracranial mass effect from increased tumour size, and elevated adrenocorticotrophic hormone (ACTH) levels. The incidence of this complication varies depending on the exact definition used. Patients with Cushing's disease who undergo bilateral adrenalectomy should have plasma ACTH levels and pituitary MRI 6 to 12 months after surgery. Therapy includes repeat surgery to debulk tumour, and radiotherapy.[126]		
treatment-related central hypothyroidism	**variable**	**high**
After pituitary surgery, patients may develop thyrotropin deficiency requiring medical replacement.[67] [109] [128] [129]		
treatment-related growth hormone deficiency	**variable**	**high**
Somatotropin deficiency may occur in between 53% and 93% of patients who undergo pituitary adenomectomy.[128] [132] Deficiency of growth hormone requires replacement.[109]		
treatment-related adrenal insufficiency	**variable**	**medium**
Transient postoperative adrenal insufficiency (defined as a morning serum cortisol of 55 nanomol/L [<2 micrograms/dL]) in patients treated with transsphenoidal surgery is an indicator of remission or cure. These patients generally have recovery of adrenal function within the first postoperative year. However, repeat pituitary surgery and occasional primary surgical therapy can result in permanent adrenal insufficiency. Radiotherapy can cause adrenal insufficiency years after therapy, necessitating pituitary adrenal axis evaluation periodically after therapy. Bilateral adrenalectomy also creates an absolute cortisol deficiency, and must be treated with replacement doses of hydrocortisone plus mineralocorticoid. Long-term adrenal insufficiency secondary to pituitary adenomectomy occurs in 3% to 53% of patients.[67] [124] [125] Steroidogenesis inhibitors can also sometimes cause adrenal insufficiency.		
surgery- or radiation-related hypopituitarism	**variable**	**medium**
Therapy for Cushing's disease, either surgery or radiotherapy, can damage normal pituitary tissue. If hypopituitarism is the result of surgical therapy, deficits generally manifest immediately after surgery. Hypopituitarism after radiotherapy can occur many years after therapy. Individuals who have received		

Complications	Timeframe	Likelihood
radiotherapy should have periodic evaluation of pituitary function to monitor for development of recurrences. Pituitary surgery may lead to deficiencies of hormones other than the adrenocorticotrophic hormone, requiring replacement with thyroid hormones, androgens or oestrogens, growth hormone, or desmopressin.[109]		
surgery-related hyponatraemia	**variable**	**medium**
Hyponatraemia is a known complication of pituitary surgery. Age, sex, tumour size, rate of decline of blood sodium, and Cushing syndrome are potential predictors of delayed symptomatic hyponatraemia.[127]		
treatment-related hypogonadism	**variable**	**medium**
Occurs in between 3% and 48% of patients undergoing pituitary adenomectomy.[67] [128] [129] [130] [131] Pituitary surgery may lead to deficiencies of hormones other than the adrenocorticotrophic hormone, requiring replacement with thyroid hormones, androgens or oestrogens, growth hormone, or desmopressin.[109]		
treatment-related diabetes insipidus	**variable**	**medium**
More than one quarter of patients who undergo surgery will develop vasopressin deficiency and rates are higher after the second surgery.[69] [133] [134] Pituitary surgery may lead to deficiencies of hormones other than the adrenocorticotrophic hormone, requiring replacement with thyroid hormones, androgens or oestrogens, growth hormone, or desmopressin.[109] Over 50% of patients with Cushing's disease treated with pasireotide develop hyperglycaemia that must be promptly managed.[92] [97]		

Prognosis

Without treatment, hypercortisolism persists and in many patients worsens. Untreated disease carries a dismal survival rate of 50% at 5 years.[113] This leads to worsening of the Cushing phenotype and increased mortality, mainly from cardiovascular disease. With therapy to normalise cortisol levels, patients have a mortality rate similar to the general population.[66] [67] Within the first year of effective therapy, many of the characteristic features such as facial plethora, striae, and supraclavicular fat pads will resolve or show marked improvement. Patients lose a significant amount of weight with improved control or resolution of diabetes and hypertension. Bone density steadily improves after hypercortisolism resolves. Despite improvement of complications in most patients, cardiovascular risk, hypertension, obesity, and decreased quality of life may persist in some patients even after biochemical cure.[11] [114] [115]

Patient-reported outcomes are scarce, but they show that decreased quality of life persists even in patients with biochemical normalisation and they are worse in Cushing's disease compared with Cushing syndrome.[116]

Pituitary adenomectomy

Outcomes are largely based on the size of the initial tumour in patients with Cushing's disease. Micro-adenomas (size <1 cm) have superior outcomes with remission rates quoted as 48% to 100% of patients. An average of approximately 32% of Cushing's disease patients, and up to 75% of Cushing's disease

patients initially submitted to pituitary surgery, will require a second-line treatment during the disease course. The long-term failure of pituitary surgery is evidently higher in patients with macro-adenomas (range, 0 to 71.4; mean, 48.8; median, 52.2) than in patients with micro-adenomas (range, 0 to 55.5; mean, 25; median, 21.2).[69] [73] [117] Patients with macro-adenomas (size >1 cm) have remission rates <65% after surgery and show recurrence rates of 12% to 45% at about 16 months.[67] [113] [118] Patients may require temporary or prolonged treatment for deficiencies of thyrotropin, gonadotrophin, growth hormone, or antidiuretic hormone and corticosteroids.

A 2018 study did not find significant differences between endoscopic and microscopic pituitary surgery in remission percentage. Although the short term recurrence was lower for endoscopic surgery, both groups had a recurrence rate of approximately 4% per person/year.[119] A 2021 study in young people with pituitary tumours found favourable outcomes and lower re-treatment rates with endonasal endoscopic surgery compared with microscopic transsphenoidal surgery.[120]

Adrenocorticotrophic hormone (ACTH)-independent Cushing syndrome

Patients who undergo unilateral adrenalectomy for a causative adrenal adenoma are uniformly cured of their disease. Recurrence in the contralateral adrenal gland is exceedingly rare. Patients with bilateral adrenalectomy will need monitoring and corticosteroid and mineralocorticoid replacement. Outlook for patients with adrenal carcinoma depends upon the stage at which it is diagnosed. Beyond surgical resection, benefit of additional treatments is debated and should be patient-specific.

Ectopic ACTH production

Encompasses a diverse group. The nature of the tumour secreting ACTH largely determines the outcomes. Many ACTH-secreting tumours are aggressive and grow rapidly. In these cases, complete resection of the tumour is difficult, and patients generally succumb to tumour-related complications. Individuals with indolent ACTH-secreting tumours often have complete tumour resection with resolution of hypercortisolism as well as symptoms.

Diagnostic guidelines

North America

Diagnosis, management, and followup of the incidentally discovered adrenal mass (https://www.cua.org/guidelines)

Published by: Canadian Urological Association **Last published:** 2023

Consensus on diagnosis and management of Cushing's disease: a guideline update (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8743006)

Published by: The Pituitary Society **Last published:** 2021

ACR appropriateness criteria: adrenal mass evaluation (https://www.acr.org/Clinical-Resources/Clinical-Tools-and-Reference/Appropriateness-Criteria)

Published by: American College of Radiology **Last published:** 2021

The diagnosis of Cushing's syndrome (https://www.endocrine.org/clinical-practice-guidelines)

Published by: The Endocrine Society **Last published:** 2008

Asia

Clinical guidelines for the diagnosis and treatment of Cushing's disease in Korea (https://www.e-enm.org/journal/view.php?doi=10.3803/EnM.2015.30.1.7)

Published by: Korean Endocrinology Society **Last published:** 2015

Treatment guidelines

United Kingdom

Endoscopic transsphenoidal pituitary adenoma resection (https://www.nice.org.uk/guidance/IPG32)

Published by: National Institute for Health and Care Excellence **Last published:** 2003

Europe

Clinical practice guidelines on the management of adrenocortical carcinoma in adults (https://www.ese-hormones.org/publications/guidelines)

Published by: European Society of Endocrinology, European Network for the Study of Adrenal Tumors **Last published:** 2018

Management of adrenal incidentalomas (https://www.ese-hormones.org/publications/guidelines)

Published by: European Society of Endocrinology; European Network for the Study of Adrenal Tumors **Last published:** 2016

Treatment of Cushing's syndrome (https://www.endocrine.org/clinical-practice-guidelines)

Published by: The Endocrine Society; European Society for Endocrinology **Last published:** 2015

International

Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement (https://academic.oup.com/jcem/article/93/7/2454/2598289)

Published by: Pituitary Society; European Neuroendocrine Association **Last published:** 2008

North America

Diagnosis, management, and followup of the incidentally discovered adrenal mass (https://www.cua.org/guidelines)

Published by: Canadian Urological Association **Last published:** 2023

NCCN clinical practice guidelines in oncology: neuroendocrine and adrenal tumors (https://www.nccn.org/guidelines)

Published by: National Comprehensive Cancer Network **Last published:** 2023

American Association of Endocrine Surgeons guidelines for adrenalectomy (https://collectedmed.com/index.php/article/article/demo_article_display/8449/82/1/1)

Published by: American Association of Endocrine Surgeons **Last published:** 2022

Consensus on diagnosis and management of Cushing's disease: a guideline update (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8743006)

Published by: The Pituitary Society **Last published:** 2021

Medical guidelines for the management of adrenal incidentalomas (https://pro.aace.com/clinical-guidance/pituitary-gonad-adrenal-and-neuroendocrine)

Published by: American Association of Clinical Endocrinologists; American Association of Endocrine Surgeons **Last published:** 2009

Asia

Clinical guidelines for the diagnosis and treatment of Cushing's disease in Korea (https://www.e-enm.org/journal/view.php?doi=10.3803/EnM.2015.30.1.7)

Published by: Korean Endocrinology Society **Last published:** 2015

Online resources

1. Algorithm for diagnosis of Cushing syndrome (https://staticweb.bmj.com/BP/CushingSyndrome/gr1_lrg.jpg) *(external link)*

Key articles

- Sharma ST, Nieman LK, Feelders RA. Cushing's syndrome: epidemiology and developments in disease management. Clin Epidemiol. 2015 Apr 17;7:281-93. Full text (https://www.dovepress.com/cushing39s-syndrome-epidemiology-and-developments-in-disease-managemen-peer-reviewed-fulltext-article-CLEP) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/25945066?tool=bestpractice.bmj.com)
- Fleseriu M, Auchus R, Bancos I, et al. Consensus on diagnosis and management of Cushing's disease: a guideline update. Lancet Diabetes Endocrinol. 2021 Dec;9(12):847-75. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8743006) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34687601?tool=bestpractice.bmj.com)
- Nieman LK, Biller BM, Findling JW, et al. Treatment of Cushing's syndrome: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2015 Aug;100(8):2807-31. Full text (https://academic.oup.com/jcem/article/100/8/2807/2836065) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26222757?tool=bestpractice.bmj.com)
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Images

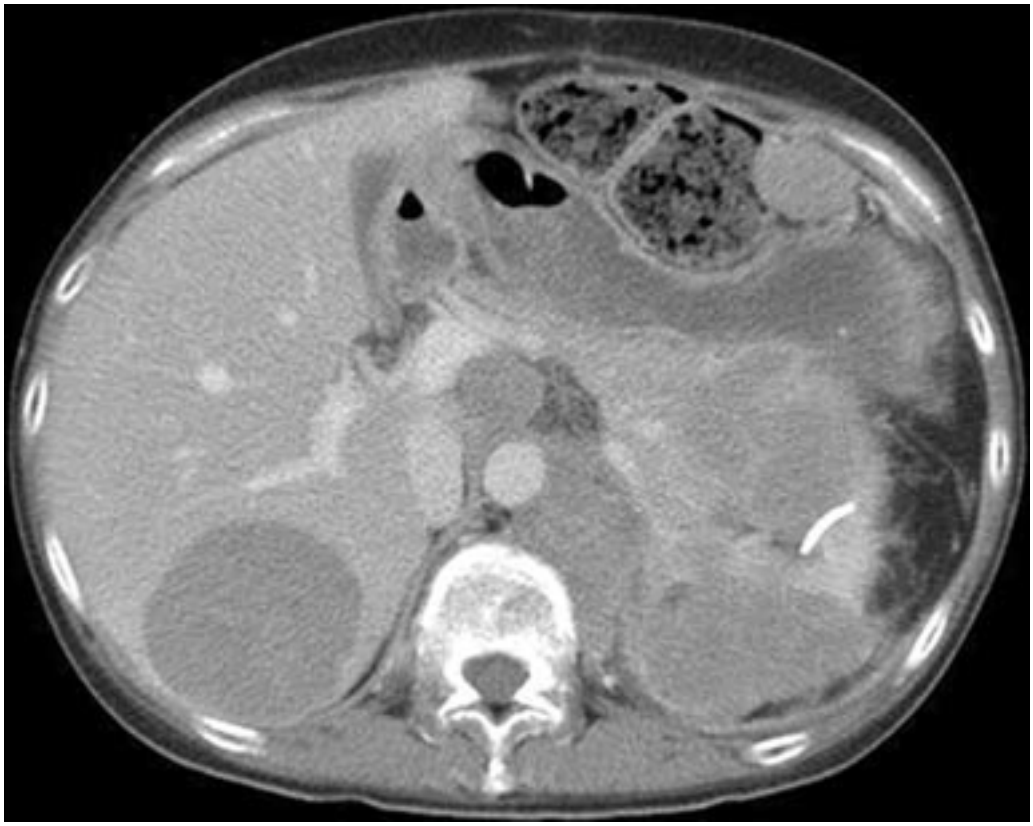

Figure 1: Abdominal computed scan showing adrenocortical tumour infiltrating the pancreas and left kidney, and metastasised to the liver, spleen, and central nodes

From BMJ Case Reports 2010; doi:10.1136/bcr.07.2009.2100

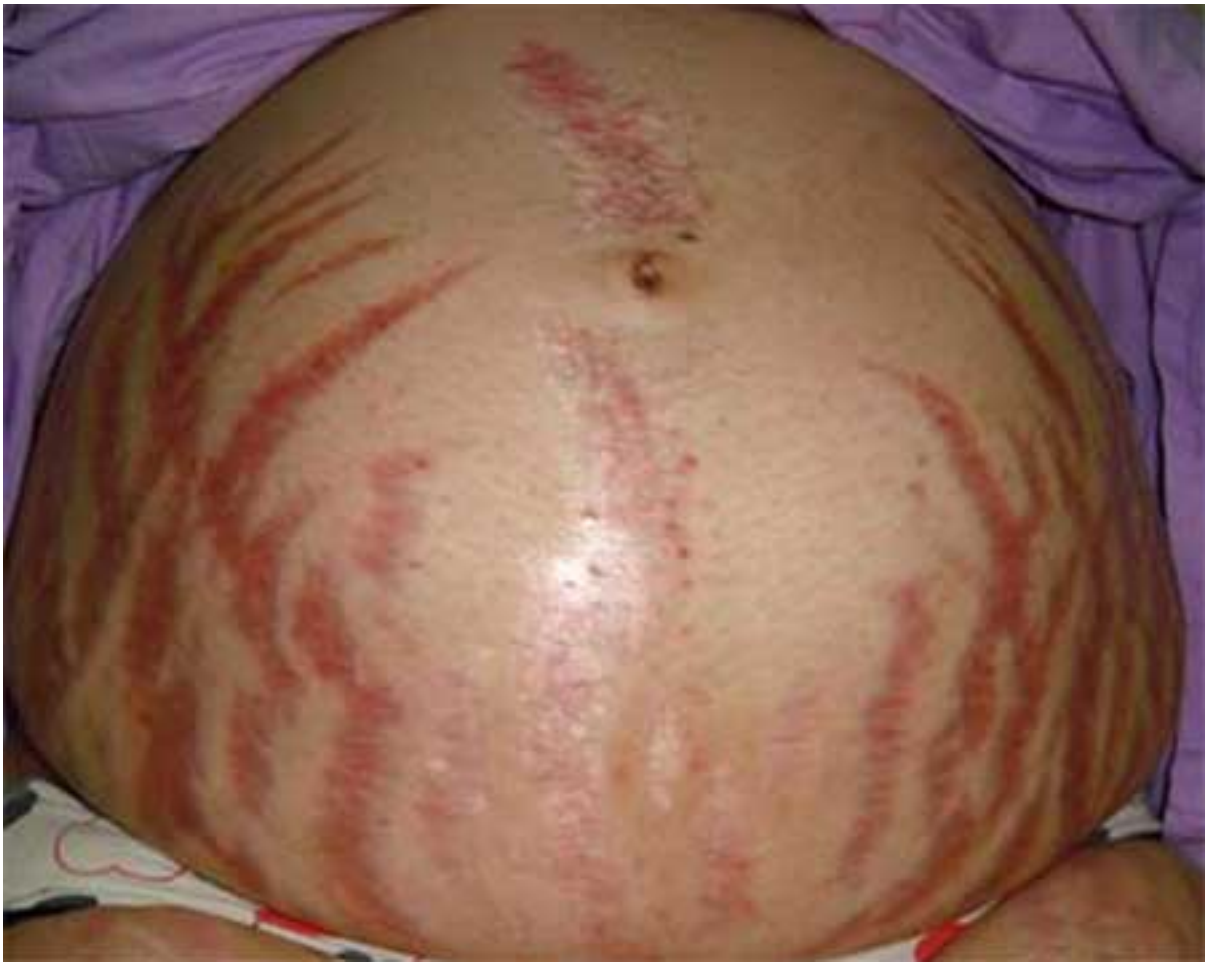

Figure 2: Abdominal striae in pregnancy

From BMJ Case Reports 2011; doi:10.1136/bcr.01.2011.3720

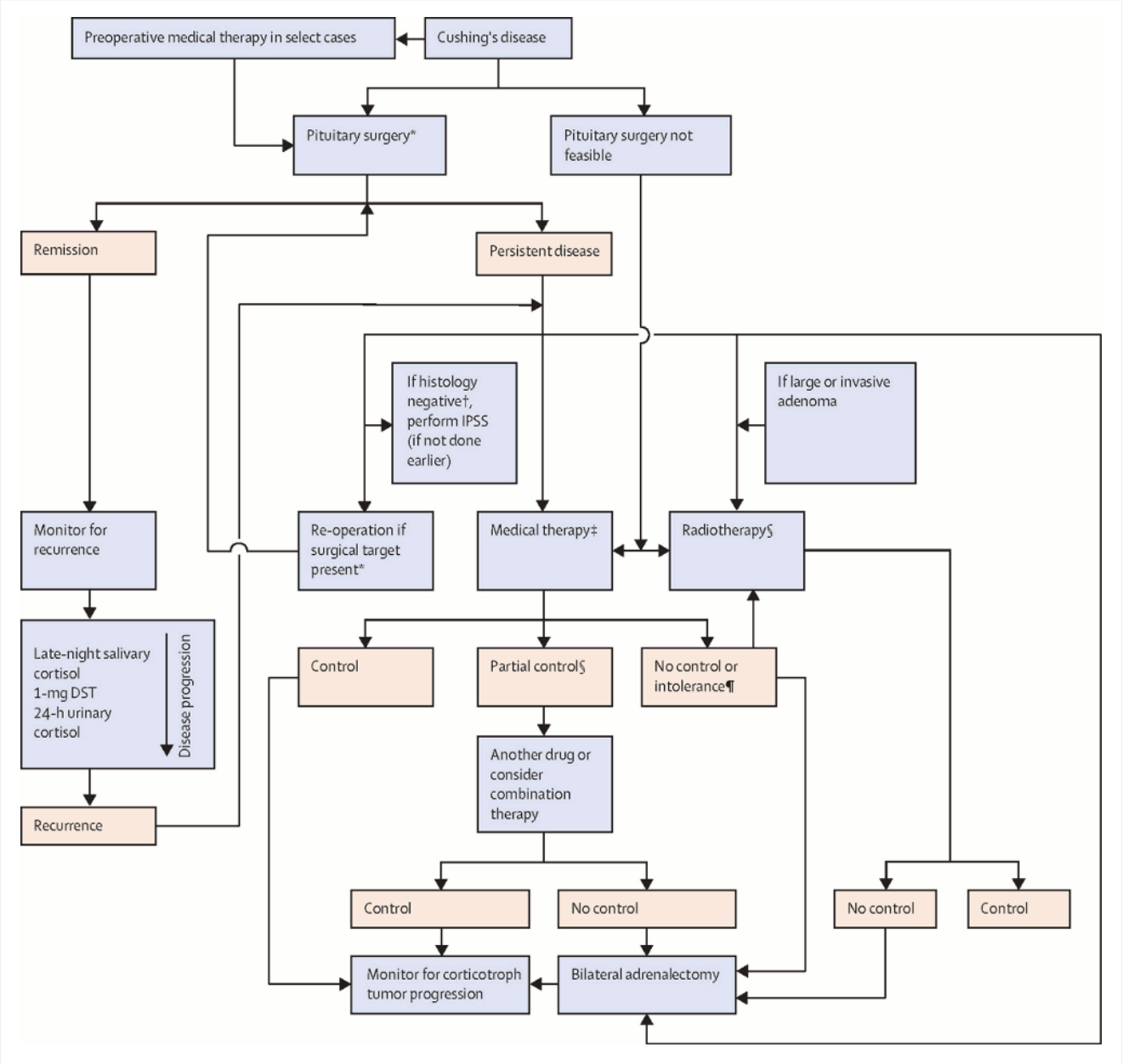

*Figure 3: Algorithm for the treatment of Cushing's disease (DST = dexamethasone suppression#est. IPSS = inferior petrosal sinus sampling. ACTH = adrenocorticotrophic hormone. *Pituitary surgery should be performed by an experienced surgeon. †Absence of ACTH-staining adenoma. §Lifelong monitoring for hypopituitarism and secondary neoplasia in the radiation field required. ¶On maximum tolerated dose of the drug)*

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This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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Contact us

+ 44 (0) 207 111 1105
support@bmj.com

BMJ
BMA House
Tavistock Square
London
WC1H 9JR
UK

BMJ Best Practice

Contributors:

// Authors:

Maria Fleseriu, MD, FACE

Professor of Medicine (Endocrinology) and Neurological Surgery
Director, Pituitary Center, Oregon Health & Science University, Portland, OR
DISCLOSURES: MF is on the Pituitary Society's Board of Directors. She holds a research grant to the University for Clinical Studies as Principal Investigator for Recordati and Strongbridge, and is an occasional Scientific Consultant for Recordati, HRA Pharma, and Sparrow. MF is an author of several references cited in this topic.

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// Peer Reviewers:

Paul M. Stewart, FRCP FMedSci

Professor of Medicine
Director of Research, College of Medical and Dental Sciences, University of Birmingham, Honorary Consultant Physician, Queen Elizabeth Hospital, Birmingham, UK
DISCLOSURES: PMS declares that he has no competing interests.

Antoine Tabarin, MD

Head
Department of Endocrinology, University Hospital of Bordeaux, Pessac, France
DISCLOSURES: AT declares that he has no competing interests.

Liliana Contrersas, MD

Chief
Endocrine Research Department, Instituto de Investigaciones Médicas A. Lanari, University of Buenos Aires and IDIM-CONICET, Buenos Aires, Argentina
DISCLOSURES: LC declares that she has no competing interests.

Philip R. Orlander, MD

Professor of Medicine
Director, Division of Endocrinology, Diabetes & Metabolism, University of Texas Medical School, Houston, TX
DISCLOSURES: PRO declares that he has no competing interests.

Mouhammed Amir Habra, MD, FACP, FACE

Assistant Professor

Contributors:

Department of Endocrine Neoplasia and Hormonal Disorders, Division of Internal Medicine, University of Texas MD Anderson Cancer Center, Houston, TX
DISCLOSURES: MAH declares that he has no competing interests.