Consensus on diagnosis and management of Cushing's disease: a guideline update

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Cushing's disease requires accurate diagnosis, careful treatment selection, and long-term management to optimise patient outcomes. The Pituitary Society convened a consensus workshop comprising more than 50 academic researchers and clinical experts to discuss the application of recent evidence to clinical practice. In advance of the virtual meeting, data from 2015 to present about screening and diagnosis; surgery, medical, and radiation therapy; and disease-related and treatment-related complications of Cushing's disease summarised in recorded lectures were reviewed by all participants. During the meeting, concise summaries of the recorded lectures were presented, followed by small group breakout discussions. Consensus opinions from each group were collated into a draft document, which was reviewed and approved by all participants. Recommendations regarding use of laboratory tests, imaging, and treatment options are presented, along with algorithms for diagnosis of Cushing's syndrome and management of Cushing's disease. Topics considered most important to address in future research are also identified.

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Introduction

Cushing's disease, the most common cause of endogenous Cushing's syndrome, is caused by an adrenocorticotropic hormone (ACTH)-secreting pituitary tumour.[1] Optimal patient outcomes require accurate diagnosis, careful treatment selection, and management of the disease and its associated comorbidities to optimise patient outcomes.[2] Notably, compared with patients with adrenal causes of Cushing's syndrome, long-term quality of life is worse for patients with Cushing's disease.[3] Since the publication of clinical guidelines in 2003,[4] 2008,[5,6] and 2015,[7] novel screening and diagnostic modalities have been identified and new treatments approved for use. These new developments highlight the need for updates to clinical guidelines on this challenging disorder.

The Pituitary Society convened a 2-day virtual consensus workshop in October, 2020, to discuss management of Cushing's disease, critically review current literature, and provide recommendations for screening and diagnosis; optimal use of and monitoring outcomes from surgery, medical therapy, and radiation therapy; and identification and management of disease-related and treatment-related complications. The focus was on pituitary, rather than adrenal or ectopic Cushing's syndrome, and overlapping topics that had been recently covered in other consensus statements or reviews were not included.

This guideline update reviews recent evidence and recommendations for clinical practice, grading the quality of the evidence and the strength of the consensus recommendations. Key considerations for use of different laboratory tests and medical therapies are presented in the tables. Consensus recommendations for the diagnosis and monitoring of Cushing's syndrome, management of Cushing's disease complications, and use of medical therapy for Cushing's disease are presented in the panels. Grading schema[8,9] for quality of evidence and strong or discretionary recommendations are presented in the appendix (p 3). Algorithms for diagnosis of Cushing's syndrome (figure 1) and management of Cushing's disease are also presented.

Recommendations for adults with Cushing's disease are presented for use in clinical practice but should be considered alongside patient-specific and disease-specific factors for personalised care. A brief section regarding unique considerations in paediatric Cushing's disease is also included.

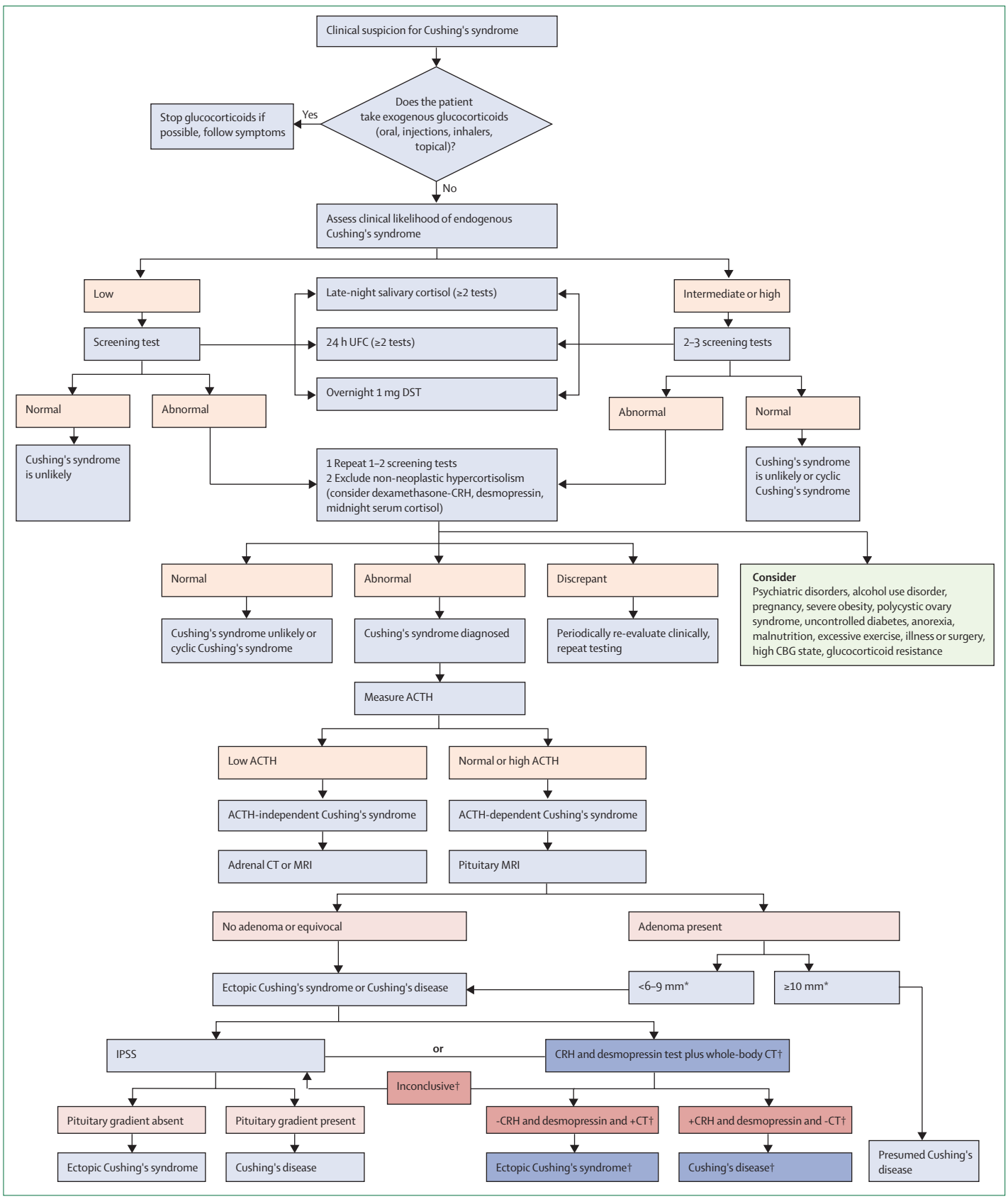
Methods

Workshop co-chairs and steering committee members identified 28 discrete topics related to Cushing's disease diagnosis, complications, and treatment to be addressed. Methods for critical review of the literature, pre-workshop lectures, and workshop discussions are described in the appendix.

Diagnosis of Cushing's syndrome: screening, confirmatory, and localisation modalities

Laboratory tests

Diagnosis of Cushing's syndrome is often delayed for years, partly because of lack of awareness of the insidious, progressive disease process and testing complexity.[10] Screening and diagnostic tests for Cushing's syndrome assess cortisol secretory status: abnormal circadian rhythm with late-night salivary cortisol (LNSC), impaired glucocorticoid feedback with overnight 1 mg dexamethasone suppression test (DST) or low-dose 2-day dexamethasone test (LDDT), and increased bioavailable


Clinical suspicion for Cushing's syndrome
Does the patient take exogenous glucocorticoids (oral, injections, inhalers, topical)?
Yes
Stop glucocorticoids if possible, follow symptoms
No
Assess clinical likelihood of endogenous Cushing's syndrome
Low
Screening test
Normal
Abnormal
Cushing's syndrome is unlikely
Late-night salivary cortisol (≥2 tests)
24 h UFC (≥2 tests)
Overnight 1 mg DST
Intermediate or high
2–3 screening tests
Abnormal
Normal
Cushing's syndrome is unlikely or cyclic Cushing's syndrome
1 Repeat 1–2 screening tests
2 Exclude non-neoplastic hypercortisolism (consider dexamethasone-CRH, desmopressin, midnight serum cortisol)
Normal
Abnormal
Discrepant
Cushing's syndrome unlikely or cyclic Cushing's syndrome
Cushing's syndrome diagnosed
Periodically re-evaluate clinically, repeat testing
Consider
Psychiatric disorders, alcohol use disorder, pregnancy, severe obesity, polycystic ovary syndrome, uncontrolled diabetes, anorexia, malnutrition, excessive exercise, illness or surgery, high CBG state, glucocorticoid resistance
Measure ACTH
Low ACTH
Normal or high ACTH
ACTH-independent Cushing's syndrome
ACTH-dependent Cushing's syndrome
Adrenal CT or MRI
Pituitary MRI
No adenoma or equivocal
Adenoma present
Ectopic Cushing's syndrome or Cushing's disease
<6–9 mm*
≥10 mm*
IPSS
or
CRH and desmopressin test plus whole-body CT†
Inconclusive†
Pituitary gradient absent
Pituitary gradient present
-CRH and desmopressin and +CT†
+CRH and desmopressin and -CT†
Ectopic Cushing's syndrome
Cushing's disease
Ectopic Cushing's syndrome†
Cushing's disease†
Presumed Cushing's disease

cortisol with 24-h urinary free cortisol (UFC; panel 1).[5,6,11,12] In this setting, sensitivity of all tests is higher than 90%; the highest sensitivity rates are obtained with DST and LNSC and the lowest with UFC. Specificity is somewhat lower than sensitivity, with LNSC being the most specific and DST and UFC the least specific.[12,13]

LNSC

The diagnostic utility of LNSC is based on the assumption that patients with Cushing's syndrome lose the normal circadian nadir of cortisol secretion;[14,15] at least two or three LNSC tests are recommended.[5,16] Patients with mild Cushing's syndrome may have LNSC just above the upper limit of normal (ULN). Sampling saliva at usual bedtime rather than at midnight could decrease false-positive results,[17] as cortisol nadir is tightly entrained to sleep onset. Liquid chromatography tandem mass spectrometry can detect both cortisol and cortisone, thereby identifying contamination from topical hydrocortisone preparations, which typically do not contain cortisone. Thus, specificity is higher when using mass spectrometry while immunoassay has higher sensitivity for Cushing's syndrome.[18] Multiple, periodic, sequential LNSC tests are particularly useful for the longitudinal surveillance needed in distinguishing patients with cyclic Cushing's syndrome who exhibit weeks to months of normal cortisol secretion interspersed with episodes of cortisol excess.[19] By contrast, LNSC should not be done in patients with disruption of the normal day and night cycle, such as night-shift workers.[14,15]

Overnight 1-mg DST

In healthy individuals, a supraphysiological dexamethasone dose inhibits vasopressin and ACTH secretion, thereby decreasing cortisol concentrations. Thus, a serum cortisol concentration of less than 1·8 µg/dL (50 nmol/L) at 0800 h in the morning after 1 mg dexamethasone given between 2300 h and midnight is considered to be a normal response.[5] A negative result strongly predicts absence of Cushing's syndrome. At higher cutoff points (eg, 5 µg/dL [138 nmol/L]), DST sensitivity is reduced.[12] Cortisol concentrations of less than 1·8 µg/dL excludes dysregulated cortisol production from an adrenal incidentaloma;[20] in this setting, values higher than 5 µg/dL generally identify patients with dysregulated cortisol secretion from an incidentaloma with overt Cushing's syndrome. False positive results might be seen with rapid absorption or malabsorption of dexamethasone due to increased gut transit time, chronic diarrhoea, or coeliac disease; from concomitant treatment with CYP3A4 inducers (eg, phenobarbital, carbamazepine, St John's wort); and from increased corticosteroid-binding globulin (CBG) concentrations caused by oral oestrogens, pregnancy, or chronic active hepatitis, which can increase total cortisol concentrations.[21–23] Measuring dexamethasone concomitantly with cortisol, using laboratory-specific ranges of expected values, can reduce the risk for false-positive results.[24,25] False-negative results are less common, typically resulting from inhibition of dexamethasone metabolism by concomitant medications such as fluoxetine, cimetidine, or diltiazem, leading to a higher biologically available dose. Decreased CBG and albumin concentrations, which can be noted in patients with concurrent nephrotic syndrome, also might produce a falsely low value.[26]

***Panel 1:* Clinical considerations and recommendations for Cushing's syndrome diagnosis and monitoring of Cushing's disease recurrence**

If Cushing's syndrome is suspected:

- Start with urinary-free cortisol (UFC), late-night salivary cortisol (LNSC), or both; dexamethasone suppression test (DST) could also be an option if LNSC not feasible
- Multiple LNSC might be easier for patient collection

If confirming Cushing's syndrome:

- Can use any test
- UFC average two-to-three collections
- LNSC (two or more tests)
- DST useful in shift workers, not in women on oestrogen-containing oral contraceptives
- Measuring dexamethasone concentration, with cortisol concentration, the morning after 1 mg dexamethasone ingestion improves test interpretability

If Cushing's syndrome due to adrenal tumour is suspected:

- Start with DST
- LNSC has lower specificity in these patients

Monitoring for recurrence:

- Consider which tests were abnormal at initial diagnosis
- LNSC most sensitive, should be done annually
- DST and UFC usually become abnormal after LNSC
- UFC is usually the last to become abnormal

Figure 1: **Algorithm for diagnosis of Cushing's syndrome**
ACTH=adrenocorticotropic hormone. CBG=corticosteroid-binding globulin; CRH=corticotropin-releasing hormone. DST=dexamethasone suppression test. IPSS=inferior petrosal sinus sampling. UFC=urinary free cortisol. *There is consensus that all patients with lesions smaller than 6 mm in diameter should have IPSS and those with lesions of ≥10 mm do not need IPSS, but expert opinions differed for lesions 6–9 mm in diameter. †This alternative option does not have clear consensus and needs further research, and this is indicated by darker boxes. Green boxes indiate points to consider; darker colours indicate less validated testing pathways.

UFC

At least two or three 24-h urine collections are advised to measure UFC to account for intra-patient variability.[5,27] One advantage with UFC over DST is that overall cortisol production is independent of CBG changes and dexamethasone metabolism or compliance. However, although calculating the mean of several collections aids

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See **Online** for appendix

in correct interpretation, random variability can be as high as 50%.[28] As with LNSC, UFC relies on accurate collection by the patient.

Sex, body-mass index (BMI), age, very high or low urinary volume, and sodium intake can all influence UFC concentrations and should be taken into account for interpretation.[29–33] Because urine volume and glomerular filtration rate strongly predict UFC, other screening tests such as LNSC might be preferred for patients with renal impairment (creatinine clearance <60 mL/min) or clinically significant polyuria (>5 L/24 h).[34,35]

Testing for non-neoplastic hypercortisolism (pseudo-Cushing's syndrome)

Psychiatric disorders, alcohol use disorder, polycystic ovary syndrome, and obesity can activate the hypothalamic–pituitary–adrenal (HPA) axis.[36,37] Such patients might also have concomitant features of Cushing's syndrome that are common in the general population (eg, weight gain) that lead to biochemical screening. DST, LNSC, and UFC can all show positive (abnormal) results in these patients with non-neoplastic clinical hypercortisolism, or so-called pseudo-Cushing's syndrome.[38] Furthermore, concomitant medications could result in steroid cross-reactivity or otherwise interfere with laboratory test results. However, these abnormal results tend to be mildly elevated; UFC is almost always within 3-fold of normal concentrations. The combined LDDT–corticotrophin-releasing hormone (CRH; Dex-CRH) test, LDDT, or the desmopressin test might be able to distinguish between ACTH-dependent Cushing's syndrome and pseudo-Cushing's syndrome.[39–41] Utility of the Dex-CRH test in this setting is based on the assumption that only patients with ACTH-dependent Cushing's syndrome will show a cortisol response to CRH after dexamethasone suppression.[42] However, test reliability can differ because of different protocols, use of ovine or human CRH in varying doses, characteristics of cortisol and ACTH assays, and patient characteristics (eg, degree of hypercortisolism, adrenal versus pituitary Cushing's syndrome, and comorbidities). Use of the desmopressin test is based on the finding that ACTH-secreting adenomas express vasopressin V1b receptors (also known as vasopressin 3 receptors), producing an increase in plasma ACTH concentration after desmopressin injection.[43] The desmopressin test has a high specificity for Cushing's disease[44] and is less complex and expensive than the Dex-CRH test, but both tests have shown good diagnostic performance in distinguishing Cushing's syndrome from pseudo-Cushing's syndrome in some studies; when both tests are done, they showed excellent agreement.[45,46]

Clinical considerations and recommendations for laboratory tests

There is no single preferred diagnostic test for Cushing's syndrome (panel 1), nor is there consensus on how to decide whether and when to test, despite attempts to develop a score for ease of diagnosis.[47] Clinical judgment and index of suspicion for Cushing's syndrome are important[48] and underscore the need to individualise decisions about timing and selection for diagnostic testing on the basis of the clinical scenario (high quality evidence, strong recommendation).

If Cushing's syndrome is suspected, any of the diagnostic tests could be useful. We recommend starting with UFC, LNSC, DST, or a combination (high quality, strong recommendation) depending on local availability; multiple LNSCs might be easier for the patient to complete (high quality, strong recommendation). If an adrenal tumour is suspected, we recommend starting with DST (moderate quality, strong recommendation) and only using LNSC if cortisone concentrations can be also reported[16,18] (moderate quality, strong recommendation; panel 1).

DST might be the preferred test for shift workers and patients with disrupted circadian rhythm due to uneven sleep schedules, but might not be reliable in women treated with oral oestrogen (high quality, strong recommendation). Measuring dexamethasone levels can be useful if a false-positive DST is suspected due to the clinical scenario (moderate quality, strong recommendation). If UFC is used, two or three collections should be obtained to evaluate variability (high quality, strong recommendation). If LNSC is used, we recommend at least two or three tests (high quality, strong recommendation). Although there were initial concerns about increased risk for infection from SARS-CoV-2 with LNSC,[49] it remains safe for laboratory personnel when used with proper precautions.[50] Bilateral inferior petrosal sinus sampling (IPSS) should not be used to diagnose hypercortisolism because the central-to-peripheral ACTH gradient in healthy controls and pseudo-Cushing's syndrome overlaps with that observed in patients with Cushing's disease[51] (high quality, strong recommendation). In classical cyclic Cushing's disease or in patients with unpredictable fluctuating cortisol concentrations, dynamic testing and localisation testing, including IPSS, should be preceded by a confirmatory LNSC or UFC to document that the patients are in the active phase (panel 1).[52]

Currently, there is no preference for mass spectrometry over immunoassay in measuring cortisol level for diagnosis to ensure that patients with mild hypercortisolism are not excluded.[18,27] However, normative data with modern assays are needed.

Non-neoplastic hypercortisolism

Non-neoplastic hypercortisolism or pseudo-Cushing's syndrome remains one of the most challenging diagnoses. Because the cause of pseudo-Cushing's syndrome varies, there is no single approach to rule it out.[53] We recommend considering the patient's clinical history, particularly the duration of symptoms, and repeating tests to avoid implementing inappropriate treatment if Cushing's syndrome is not present (low quality, discretionary recommendation). In most cases,

patients have mild hypercortisolism and can be monitored for 3–6 months to see whether symptoms resolve; treatment of the underlying condition (such as depression) can restore normal HPA axis function and cortisol concentrations (low quality, discretionary recommendation). Standard diagnostic testing is unreliable in this population. LDDT or serial LNSC tests over time correlate with the clinical picture (low quality, discretionary recommendation). Desmopressin is easy to use and easily administered in an outpatient setting. Dex-CRH in this setting could be valuable, but published diagnostic accuracy results have varied; use at an expert centre with measurement of dexamethasone concentrations is advised (moderate quality, strong recommendation),[54] as are cortisol cut-off adjustments in patients with severe obesity. CRH is not currently available in the USA, Canada, Brazil, Argentina, Mexico, and some other countries.

Imaging and tumour localisation

MRI is the imaging method of choice for detecting ACTH-secreting pituitary adenomas. However, in part because most lesions are very small, with use of standard 1·5T MRI only approximately 50% of microadenomas are clearly depicted.[55]

Technical refinements, including spoiled gradient-recalled (SPGR) acquisition echo with 1 mm slice intervals, fluid attenuation inversion recovery,[56] and constructive interference in the steady state, might enhance detection, and variants of T1-weighted turbo spin echo sequences and use of ultra-high-field 3T and 7T magnets allow improved localisation of microadenomas.[57–60] Nevertheless, approximately a third of scans in patients with Cushing's disease still remain negative,[61] and higher resolution with 3T or 7T magnets can increase the risk of detecting incidentalomas potentially unrelated to the disorder.

Tumour size does not necessarily correlate with degree of hypercortisolism in Cushing's disease. In fact, patients with larger adenomas can present with milder hypercortisolism.[62]

PET has been explored as an alternative to, or in combination with, MRI for localisation of corticotroph adenomas. ^{18}F-fluoro-deoxy-glucose (^{18}F-FDG) PET/CT was largely comparable with standard fast-spin echo MRI in detecting pituitary lesions in one series,[63] and a separate study found that both standard-spin echo MRI and high-resolution ^{18}F-FDG PET were inferior to SPGR MRI.[64] Prior CRH stimulation can increase ^{18}F-FDG uptake and thus increase detection.[65] PET co-registration with volumetric MRI (PET/magnetic resonance coregistration) combines functional and anatomical imaging, and ^{11}C-methionine can permit more accurate localisation of sites of radiotracer uptake.[66] In one series, this technique correctly localised corticotroph adenomas in patients with de novo disease and persistent or recurrent hypercortisolism after primary surgery, most of whom had negative or equivocal standard-spin echo MRI.[67] However, this approach is not available or approved in most countries. Alternative strategies (eg, targeting CRH-1 receptors on corticotroph tumours) have also recently been proposed, but require further study.[68]

Clinical considerations and recommendations for imaging and tumour localisation

MRI remains the imaging modality of choice for ACTH-secreting pituitary adenomas (high quality, strong recommendation). We suggest 3T instead of 1·5T MRI where available (low quality, discretionary recommendation). 7T MRI is not widely available and there is currently no justification for re-imaging on 7T MRI if no tumour is detected with 1·5T or 3T MRI.

It is likely that functional imaging will ultimately prove to be a better approach than MRI alone. However, more data are needed to define use of different ligands in various clinical settings. Although advanced imaging technologies are available in some centres of excellence, the benefit of referring all patients for further imaging after 3T MRI remains unknown.

Distinguishing between Cushing's disease and ectopic ACTH-dependent Cushing's syndrome

In patients with Cushing's disease, glucocorticoid receptors typically retain the ability to inhibit ACTH secretion in the presence of high dexamethasone doses, and vasopressin V2 and V1b (V3) receptors, along with CRH receptor, are all overexpressed. By contrast, most (but not all) ectopic ACTH-secreting tumours do not express these receptors. Accordingly, desmopressin and CRH stimulation testing have proven useful in distinguishing between pituitary and ectopic tumors.[69–71] Increased plasma ACTH and increased cortisol concentrations after CRH or desmopressin administration usually indicates Cushing's disease.[72–76] Using more than one dynamic test might further improve clinical accuracy.[77] Nevertheless, well differentiated neuroendocrine tumours can also express any or all of these receptors, potentially leading to false-positive results. High-dose (8 mg) DST, although it has low accuracy overall, is still used in some countries. None of the diagnostic tests have 100% specificity and results can be discordant in up to a third of patients;[5,6] differences in type of ectopic tumour, as well as patient age, sex, and severity of hypercortisolism can all influence outcomes.

IPSS, which measures ACTH in pituitary versus peripheral venous drainage, has long been the gold standard to reliably exclude ectopic ACTH production[78,79] and should preferably be performed in a specialised centre because of potential patient risk. A central-to-peripheral ACTH gradient less than 2 before or less than 3 after stimulation suggests an ectopic tumour; however, both false-negatives and false-positives have been reported. Prolactin measurement might improve diagnostic accuracy and it is essential that the patient is hypercortisolaemic at the time of IPSS.[80]

A non-invasive approach using a combination of three or four tests, specifically CRH and desmopressin stimulation plus MRI, followed by whole-body CT if diagnosis is equivocal, correctly diagnosed Cushing's disease in approximately half of patients in one series, potentially eliminating the need for IPSS.[81] A positive CT scan, negative CRH and desmopressin stimulation, and negative MRI, had a negative predictive value of 100% for Cushing's disease. Currently, this combination of laboratory and imaging testing as a non-invasive approach to distinguish between pituitary and ectopic ACTH-secreting tumours is likely to be limited to specialised centres.[82]

^{68}Ga-DOTATATE is a modified (Tyr3)-octreotide molecule covalently linked to 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) combined with the radioactive ^{68}Ga isotope. The radiopharmaceutical, with a half-life of approximately 1 h, binds to somatostatin receptors with affinity similar to octreotide and can be used as a tracer in PET imaging of ectopic ACTH-secreting neuroendocrine tumours.[83] ^{68}Ga-DOTATATE localises about 65% of these tumours,[84] including those not seen or not definitively identified on cross-sectional imaging, and images are sharper than with single photon ^{111}In-DTPA-pentetreotide, with greater sensitivity for small tumours.[85,86] False-positives can occur because of chronic inflammation, and a positive scan does not definitively prove that the neuroendocrine tumour is the source of ACTH, but ^{68}Ga-DOTATATE imaging can be useful in guiding clinical management.[87]

The ^{68}Ga isotope is typically derived from decaying ^{68}Ge and the worldwide supply of ^{68}Ge is being exhausted. The ^{68}Ga isotope, if it can be generated locally via a cyclotron, or ^{64}Cu, which has a longer 12·7-h half-life and can be centrally produced, could be used as alternative DOTATATE, DOTATOC, or DOTANOC conjugates.[88]

Clinical considerations and recommendations for distinguishing between Cushing's disease and ectopic ACTH-dependent Cushing's syndrome

No single laboratory test or combination of tests can absolutely differentiate between pituitary and ectopic ACTH-secreting tumours (high quality, strong recommendation). We recommend using both the clinical context and test results to guide management (high quality, strong recommendation). When prompt access to brain MRI is not available, neck-to-pelvis thin-slice CT scan is useful if suspicion is high for ectopic ACTH syndrome, such as in a male patient with very high UFC, profound hypokalaemia, or both[81] (low quality, discretionary recommendation).

If a pituitary tumour with a diameter of 10 mm or larger is detected on MRI and dynamic testing results are consistent with Cushing's disease, IPSS is not necessary for diagnosis (moderate quality, strong recommendation). As it is possible that a pituitary lesion detected on MRI is an incidental nonfunctioning adenoma or other sellar mass and the ACTH source is ectopic, clinical presentation should always be considered. Some studies suggest this is true for lesions larger than 6 mm, but not all expert centres use this lower cutoff. There was consensus that all patients with lesions less than 6 mm should have IPSS and those with lesions of 10 mm or larger do not need IPSS (moderate quality, strong recommendation). Expert opinions differ regarding tumors 6–9 mm, but the majority recommended IPSS to confirm the diagnosis in this circumstance (moderate quality, discretionary recommendation). Notably, some differences between centres and countries are based on interventional radiology availability. Prolactin measurement can be useful in ruling out a false-negative IPSS (moderate quality, discretionary recommendation). Although IPSS has high diagnostic accuracy for localisation to the pituitary gland, it is not sufficiently reliable for tumour lateralisation to the right or left side of the gland (moderate quality, strong recommendation).

A non-invasive alternative using high-dose DST and CRH stimulation test predicts Cushing's disease if both tests are positive.[89] However, if tests are discordant, IPSS is necessary (low quality, discretionary recommendation). Emerging data suggest that CRH and desmopressin testing with pituitary MRI followed by whole-body CT scan might be a reliable alternative, if assessed by an experienced multidisciplinary team (very low quality, discretionary recommendation).

Complications of Cushing's disease

Strategies for Cushing's disease management should consider how comorbidities and complications associated with Cushing's disease might compromise patient health and quality of life. Comorbidities should be addressed in many cases concomitant with or even before Cushing's disease-specific treatments to restore normal cortisol levels. Clinical considerations and recommendations regarding complications of Cushing's disease are summarised in panel 2.

Hypercoagulability

Hypercoagulability in Cushing's syndrome resulting in increased risk of thromboembolic events is paradoxically coupled with an increased bleeding tendency due to skin atrophy and capillary fragility.[90,91] Most patients show an activated coagulation cascade, including shortened activated partial thromboplastin time and increased fibrinogen, von Willebrand factor, and factor VIII, as well as impaired fibrinolysis mediated by elevated plasminogen activator inhibitor-1 and antiplasmin concentrations. Increased thrombin, thromboxane A2, and platelets, with a compensatory increase in anti-coagulation factors such as vitamin K-dependent protein C and vitamin K-dependent protein S, have also been implicated in hypercoagulability.[92,93]

The incidence of venous thromboembolic events (VTE) in patients with endogenous Cushing's syndrome is more than ten times higher versus those with nonfunctioning pituitary adenomas undergoing surgery[94] with an odds ratio (OR) of 17·82 (95% CI 15·24–20·85) compared with

Panel 2: Recommendations regarding complications of Cushing's disease

Hypercoagulability

- There is currently no standard practice for preoperative or postoperative thromboprophylaxis in patients with Cushing's disease. Some experts pause oestrogen therapy in women who are awaiting surgery, but care should be taken if it was being used as contraception, because pregnancy also is associated with increased risk of thrombosis (low quality, discretionary recommendation)
- Prophylactic anticoagulation should be considered for patients at risk for venous thromboembolic events, 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 concentrations or cortisol over-replacement in patients with adrenal insufficiency (moderate quality, strong recommendation)
- Early postoperative ambulation and use of compression stockings should be encouraged for all patients (high quality, strong recommendation)
- If thromboprophylaxis is administered, there was strong consensus for preference of low molecular weight heparin over oral anticoagulants given the long half-life of the latter and the absence of therapy to reverse their effect, which could be especially concerning in the preoperative setting (low quality, discretionary recommendation)
- Anticoagulants could be discontinued before surgery to minimise intraoperative bleeding risk, although the timing of when to stop and when to reinitiate after surgery is unclear (low quality, discretionary recommendation)
- Among meeting participants, recommended anticoagulation duration in the preoperative setting ranged from 2–4 days to 1–2 weeks, and in the postoperative setting from 1–2 days of the hospital stay up to 2–4 weeks, or even longer, to 2–3 months (low quality, discretionary recommendation)
- Thromboprophylaxis should not be routinely used in paediatric patients because of bleeding risk but is reserved for selected patients

Cardiovascular disease

- Evaluate, monitor, and treat according to current guidelines for patients at high risk of cardiovascular disease (high quality, strong recommendation)
- Management approach should be individualised (high quality, strong recommendation) on the basis of the complications present (eg, hypertension or hyperlipidaemia) and care should be coordinated with primary care and cardiology physicians as needed (very low quality, discretionary recommendation)

Bone disease

- Risk assessment for bone loss and fracture recommended in all patients (high quality, strong recommendation)
- Given the risk for fracture even in patients without osteoporosis, standard dual X-ray absorptiometry alone may not be sufficiently informative; bone quality (microscanner or trabecular bone score) or morphometric vertebral assessment is recommended where available (high quality, strong recommendation) and can be useful in detecting subclinical fractures (high quality, strong recommendation), but might not be practical for all patients. The FRAX tool to assess fracture risk is not validated for Cushing's disease
- Monitor and follow-up as for all adult high-risk populations (high quality, strong recommendation)
- Consider conventional osteoporosis treatments (eg, bisphosphonates) for patients with persistent Cushing's disease, even if bone mineral density is normal, because of increased fracture risk due to cortisol excess (high quality, strong recommendation)

Growth hormone deficiency

- There is currently no standard practice for whether, when, and how to test for growth hormone deficiency in adults with Cushing's disease. As postoperative hypothalamic–pituitary–adrenal (HPA) axis recovery is often delayed, we recommend waiting at least 6–12 months after surgery before considering growth hormone deficiency assessment (moderate quality, strong recommendation)
- Patients with macroadenomas and more aggressive surgical resection are at increased risk of hypopituitarism; patients with three or more pituitary hormone deficiencies are more likely to have growth hormone deficiency and do not need dynamic testing (high quality, strong recommendation)
- Serum insulin-like growth factor I concentration alone is not likely to be a reliable indicator of growth hormone deficiency, because concentrations can be in the lower half of the normal range.
- Accessibility of growth hormone replacement can be an important factor in determining testing and treatment considerations. If growth hormone replacement is implemented earlier than 2 years after pituitary surgery, we recommend retesting periodically to determine whether growth hormone secretion has normalised upon HPA axis recovery (moderate quality, strong recommendation)
- As Cushing's syndrome-associated myopathy does not always spontaneously resolve during remission, physical rehabilitation is recommended for all patients (low quality, discretionary recommendation).
- In children, evaluate for growth hormone deficiency 3–6 months after surgery and immediately initiate growth hormone replacement if needed to ensure proper growth

the healthy population.[92] VTE risk persists in the first few months after Cushing's disease surgery, indicating that hypercoagulability is not immediately reversible with cortisol normalisation.[92,95,96] At 30 days after adrenalectomy, VTE risk was 3·4–4·75%,[96] and the OR for thromboembolic events after bilateral adrenalectomy in a longer-term study was 3·74 (95% CI 1·69–8·27).[95] In a series of 17 patients, biochemical remission following short-term medical therapy (with various combinations of pasireotide, cabergoline, and ketoconazole) also did not seem to reverse the risk or induce changes in pro-anticoagulation factors; pulmonary embolism occurred in two patients with a marked UFC decrease.[90,97]

Data from retrospective studies[98,99] indicate that thromboprophylaxis can decrease the incidence of postoperative VTE, particularly when extended to 30 days. Surveys indicate increased awareness of the need for thromboprophylaxis and increased anticoagulation use in clinical practice,[100] but strategies to identify patients most likely to benefit are still being developed.[101]

Cardiovascular disease

Patients with Cushing's disease show an adverse cardiovascular disease risk profile that may persist even after successful treatment.[102–105] Visceral, subcutaneous, and total fat can decrease after remission, although most patients remain with overweight or obesity.[106] Type 2 diabetes is present in up to 30% of patients and dyslipidaemia, and low HDL, high LDL, and high triglycerides were reported in 16–64% of cases at diagnosis. In many patients, but not all, type 2 diabetes resolves after remission.[107] Structural cardiovascular changes improve, including left ventricular hypertrophy, concentric remodeling, dilated cardiomyopathy, increased intima media thickness, and increased formation of atherosclerotic plaques, as well as their clinical manifestations, including hypertension and heart failure, but might not fully resolve despite remission of hypercortisolism.[108]

Myocardial infarction, stroke,[109,110] and other vascular events are a primary cause of increased standardised mortality ratio (4·1–16·0) in patients with active or persistent Cushing's disease.[111] Most studies show these rates do not entirely normalise,[110,112] but are lowered upon remission, and in one study, patients in remission after a single pituitary surgery had a normal standardised mortlity ratio at 10 years.[113] Screening and risk assessment for cardiovascular risk factors before and after surgery is therefore essential.[114]

Bone disease

Skeletal fragility is a frequent and early complication of hypercortisolism, and fractures could be the first clinical manifestation of the disease. Vertebral fractures occur in 30–50% of patients, largely correlating with hypercortisolism severity.[115] Suppression of the growth hormone–insulin-like growth factor I (GH–IGF-I) and hypothalamic–pituitary–gonadal axes, as well as altered parathyroid hormone pulsatility, lead to decreased osteoblast number and function, as evidenced by decreased serum concentrations of bone formation markers including osteocalcin and alkaline phosphatase.[116] Dual X-ray absorptiometry of the lumbar spine might show low bone mineral density (BMD), but fractures can occur even in patients with BMD in the normal or osteopenic range.[117] Although BMD increases are reported after hypercortisolism resolution, some patients show persistently high fracture risk, with men at higher risk than women. Conventional osteoporosis treatments, such as bisphosphonates, as well as supportive treatment with vitamin D and calcium, can induce a more rapid improvement in BMD than cortisol normalisation alone, and could be useful in patients with persistent postsurgical hypercortisolism to prevent further bone loss.[118] Data about the role of specific bone treatments for patients with osteopenia who are in remission after Cushing's disease treatment are scarce.

Growth hormone deficiency

Glucocorticoids, both endogenous and exogenous, inhibit growth hormone secretion, thereby decreasing IGF-I production by the liver in patients with Cushing's syndrome.[119,120] Although growth hormone production can be fully restored in most patients after successful therapy and recovery of the HPA axis, even years after remission,[121] persistence of growth hormone deficiency can potentially worsen hypercortisolism complications such as bone loss, myopathy, and memory deficits.[122] Using the insulin tolerance or glucagon stimulation test, prevalence of growth hormone deficiency in adults varies with timing of the diagnosis, ranging from 50–60% when testing was done within 2 years after surgery to 8–13% when done more than 2 years after surgery.[121,123] A prevalence rate of 65% was observed with the GHRH-arginine test after a median remission time of 3 years after surgery,[124] whereas 36% of patients were diagnosed with growth hormone deficiency at 99 months after remission post-radiotherapy.[123] Prevalence using the macimorelin stimulation test is not known.[120] Notably, IGF-I is an insensitive screening test for diagnosing growth hormone deficiency in adults.[124]

Compared with other causes of growth hormone deficiency, growth hormone deficiency in patients with Cushing's syndrome is more common in women and young patients; generally, these patients have a higher prevalence of type 2 diabetes, hypertension, low bone mass, fractures, and worse quality of life.[125–127] Myopathy might be partially related to growth hormone deficiency among patients in remission. Although preoperative IGF-I concentrations during active Cushing's syndrome did not predict long-term myopathy risk, low 6-month postoperative IGF-I concentrations strongly predicted more severe long-term muscle atrophy and weakness after Cushing's syndrome remission.[128]

Growth hormone replacement ameliorates several complications associated with metabolic syndrome and

risk for cardiovascular and cerebrovascular disease. Studies show decreased bodyweight, waist circumference, and total and LDL-cholesterol, as well as quality of life and BMD improvement. Conversely, in patients with pre-existing glucose intolerance, replacement can worsen glucose metabolism.[125–127,129–131] Growth hormone replacement has not yet been shown in randomised, prospective trials to reverse metabolic syndrome and cardiovascular or cerebrovascular complications.[126]

Other complications

Increased risk of infection,[114] dysfunction of one or more pituitary axes such as central hypothyroidism,[132] gonadal function impairment, infertility, and other complications can be seen in patients with Cushing's disease. Physical and psychological morbidity commonly affects quality of life, even after successful treatment in some patients. Persistence of several features associated with prior hypercortisolism, including affective disorders, cognitive dysfunction, and negative illness perception can have a sustained effect on patients' wellbeing.[133] Proximal myopathy is characteristic of Cushing's syndrome and may persist despite biochemical remission.[134,135] The pathology is multifactorial, including protein degradation through the forkhead box O3 pathway, as well as accumulation of intramuscular fat and inactivity-associated muscle atrophy.[135] Furthermore, hypercortisolism remission can induce exacerbation of pre-existing autoimmune disorders.

Because these complications have been the subject of recent guidelines[136] and reviews,[102,134] they were not specifically addressed at the workshop.

Initial treatment of Cushing's disease and monitoring for recurrence

Pituitary surgery

Transsphenoidal surgery is recommended as first-line therapy for patients with Cushing's disease.[6,7] Remission, typically defined as postoperative serum cortisol concentrations lower than 55 nmol/L (<2 µg/dL), is seen in approximately 80% of patients with microadenomas and 60% with macroadenomas if the procedure is performed by an experienced surgeon.[137–140] Patients in remission require glucocorticoid replacement until HPA axis recovery.[7,136] As remission could be delayed, monitoring until postoperative cortisol nadir can usually identify such cases.[141,142] Occasionally, patients with mild hypercortisolism, cyclic Cushing's disease, or those treated medically before surgery can achieve remission without marked postoperative hypocortisolism. Treatment at a high-volume centre by an experienced surgeon and tumour characteristics such as detection on MRI, noninvasiveness, and size smaller than 10 mm appear to correlate with increased remission rates;[138,143] whether there is a potential incremental benefit with an endoscopic approach for macroadenomas remains unclear.[144,145] Overall, complication rates are low, with more experienced surgeons having even lower rates than less experienced surgeons.[146,147] New-onset hypopituitarism (in approximately 10% of patients), as well as permanent diabetes insipidus, CSF leak, and VTE (in <5% of patients), are the most common complications; peri-operative mortality is <1%.[143,144]

How to measure surgical expertise for Cushing's disease remains unclear. Hospitals that limit the number of neurosurgeons performing transsphenoidal surgery and therefore increase surgeon experience show better outcomes and fewer complications, compared with other hospitals, as well as shorter postoperative length of stay, and lower costs. Among neurosurgeons who perform transsphenoidal surgery, survey data demonstrate that those who have done more than 200 transsphenoidal surgeries have the lowest complication rates.[148–151] Regionalised neurosurgery teams of four or five experts per 2·5–5 million inhabitants could potentially allow for optimal outcomes, reduced costs, and increased quality of care overall.[149,152]

Clinical considerations and recommendations for pituitary surgery

We recommend patients with Cushing's disease undergo surgery in specialised pituitary tumour centres of excellence wherever possible (high quality, strong recommendation).[152] Surgery should be done by an experienced pituitary neurosurgeon with follow-up by a multidisciplinary team including a pituitary endocrinologist (high quality, strong recommendation). Outcomes of pituitary surgery and cost-effectiveness (low quality, discretionary recommendation) should be reported and be made publicly available.

Monitoring for recurrence

Recurrence after successful pituitary surgery is characterised as the reappearance of clinical and biochemical features of hypercortisolism after initial remission. Low or undetectable cortisol concentrations in the immediate postoperative period is a defining criterion of remission, but does not necessarily predict lack of recurrence;[153] some patients who show early remission with very low (<2–5 µg/dL) postoperative cortisol concentrations might experience recurrence later.[154] Published recurrence rates vary between 5% and 35%, with half of recurrences appearing within the first 5 years after surgery and half after up to 10 years or more.[137,155–157]

Lifelong monitoring for recurrence is required (panel 1).[158] In patients who responded preoperatively to desmopressin, early postoperative loss of response to desmopressin with or without dexamethasone or CRH could predict recurrence risk,[70,159–165] but is not consistently used or recommended by most experts.

Compared with use in the initial diagnosis of Cushing's syndrome, LNSC, 1-mg DST, UFC, and desmopressin

	Cutoff*	Sensitivity (%)	Specificity (%)	Advantages and instructions for testing	Disadvantages and pitfalls
Diagnosis					
1 mg dexamethasone suppression test	1·8 µg/dL (50 nmol/L)	98	81	High negative predictive value; easy for health-care provider to administer	False positives common; variable dexamethasone metabolism can confound results; oral oestrogen can increase corticosteroid-binding globulin
24-h urinary-free cortisol	Assay-specific reference range	91	81·5	Wide range for normal values	Cumbersome for patient to undertake; variability could be 50% between samples, thus 2–3 collections are needed
Late-night salivary cortisol	Assay-specific reference range	97	97·5	Easy for patient to perform; patients should be cautioned not to eat, drink, smoke, or brush their teeth for 15 min before collecting saliva samples	Intra-patient variability; cut-offs vary substantially based on reference laboratory; potential for contamination with topical hydrocortisone; not available in all centres
Monitoring for recurrence					
Late-night salivary cortisol	0·27 µg/dL (7·5 nmol/L)	75–90	93–95	In most patients late-night salivary cortisol is abnormal earlier than dexamethasone suppression test and urinary-free cortisol	Intra-patient variability; can be normal despite recurrence
24-h urinary-free cortisol	1·6 × ULN	68	100	Direct reflection of bioavailable cortisol	Approximately 50% intra-patient variability; last test to show abnormal results
Desmopressin test	Absolute cortisol increments of 7·0–7·4 µg/dL from baseline†	68	95	Earliest test to show positive results in some studies; predicts presence of corticotroph tumour; can become positive before clinical adenoma recurrence	Dynamic labour-intensive testing
1 mg dexamethasone suppression test	1·8 µg/dL (50 nmol/L)	NA	NA	Likely to be abnormal before 24-h urinary-free cortisol	Limited evidence specifically assessing utility for recurrence

ULN=upper level of normal. NA=not available. ACTH=adrenocorticotropic hormone. *Cutoffs specified are for adults. Some experts recommend using the same cutoffs for initial diagnosis and recurrence. †Some studies use ACTH absolute cutoffs or increments.

Table 1: **Laboratory tests for Cushing's syndrome diagnosis and monitoring for Cushing's disease recurrence**[12,13,158,166]

tests have a lower sensitivity for recurrence, but specificity is high (table 1).[158] LNSC can detect postoperative elevated cortisol concentrations earlier than 1-mg DST, and UFC is usually the last test to show abnormal findings in patients who recur.[166,167] Thus, LNSC could allow for earlier intervention, but serial tests are advised due to wide variability in results.[167–170]

Evaluation for recurrence should begin after HPA axis recovery, and then annually or sooner if there is clinical suspicion.[171,172] In practice, however, clinical manifestations and biomarkers can be discordant. Moreover, diagnosis of early recurrence presents the additional challenge about when and how to intervene with treatment.[171,172]

Clinical considerations and recommendations for monitoring recurrence

We recommend lifelong monitoring for recurrence of Cushing's disease (moderate quality, strong recommendation). Postoperative dynamic testing can potentially predict recurrence (low quality, discretionary recommendation), but its utility in clinical practice remains to be established as some patients with low predicted likelihood of recurrence can recur many years later.

Among the tests available, LNSC is the most sensitive for detecting recurrence and should be done annually after HPA axis recovery postoperatively (moderate quality, strong recommendation). LNSC usually shows abnormal results before DST and UFC,[166,167] although monitoring for recurrence should also take into consideration which specific tests showed abnormal result for an individual patient at initial diagnosis (moderate quality, strong recommendation). If only slight biochemical abnormalities are seen without clinical features of hypercortisolism, close monitoring with repeat testing and treatment of comorbidities rather than treatment of the underlying disorder can be considered (low quality, discretionary recommendation).

Repeat pituitary surgery

Repeat transsphenoidal surgery can be considered in patients with biochemical evidence of recurrent Cushing's disease with visible tumour on MRI.[139,173–176] At selected expert centres where successful reoperation has been reported despite the absence of detectable adenoma on MRI, either ACTH-staining adenoma on pathology or a central ACTH gradient on IPSS at initial operation was often present.[174,175]

Tumour factors, including size and presence of extrasellar extension, should be considered regarding eligibility for reoperation, and neurosurgeon experience probably plays a role in achieving good results.[155,156,177] Remission rates after reoperation vary widely in the literature, ranging from 37% to 88%, at least in part because of different remission criteria and follow-up duration.[174] Although some studies have reported a substantially higher incidence of both surgical (eg, CSF leak, meningitis) and endocrinological complications (eg, diabetes insipidus and hypopituitarism) with repeat versus initial surgery, serious morbidity is less likely in experienced hands.[155,156]

Clinical considerations and recommendations for repeat pituitary surgery

If there are no contraindications for surgery, we suggest repeat transsphenoidal surgery in patients with biochemical evidence of recurrent Cushing's disease if tumour is evident on MRI, especially if the first surgery was not done in a pituitary tumour centre of excellence (low quality, discretionary recommendation). If MRI

	Commonly used doses	Efficacy	Adverse effects	Key considerations
Adrenal steroidogenesis inhibitor				
Ketoconazole[179,181–187]	400–1600 mg total per day, orally, given twice or three times a day	Retrospective studies: approximately 65% of patients had UFC normalisation initially, but 15–25% escape	Gastrointestinal disturbances, increased liver enzymes, gynecomastia, skin rash, adrenal insufficiency	EMA-approved for treatment of endogenous Cushing's syndrome, off-label use in USA; increasing doses may be needed to counter escape; needs gastric acid for absorption (avoid proton-pump inhibitors); decrease in testosterone would be preferred in women, men need follow-up for hypogonadism; risk of serious hepatotoxicity, mostly transient but regular liver function test monitoring required; risk of QTc prolongation; careful review of other medications for potential drug–drug interactions is essential
Osilodrostat[181–183,188–192]	4–14 mg total per day, orally, given twice a day as maintenance dose; some patients require lower starting doses at 2 mg per day; 30 mg, twice a day maximum	Phase 3 randomised withdrawal study showed 86% UFC normalisation	Increased androgenic and mineralocorticoid precursors (hirsutism, hypertension, hypokalaemia), gastrointestinal disturbances, asthenia, adrenal insufficiency	FDA-approved for patients with Cushing's disease in whom pituitary surgery is not an option or has not been curative; EMA and Japan have approved for treatment of endogenous Cushing's syndrome; not yet widely available; rapid decrease in UFC; risk of hypocortisolism, hypokalaemia, and QTc prolongation; 11-deoxycortisol can cross-react in cortisol immunoassays; careful monitoring for hyperandrogenism in women
Metyrapone[179,181,187,193–197]	500 mg to 6 g total per day, orally, given three or four times a day	UFC normalisation in retrospective studies approximately 70%; in a prospective study, 47% at week 12	Increased androgenic and mineralocorticoid precursors (hirsutism, hypertension, hypokalaemia), gastrointestinal disturbances, adrenal insufficiency	EMA-approved for treatment of endogenous Cushing's syndrome, off-label use in USA; rapid decrease in UFC, typically in first month; 11-deoxycortisol can cross-react in cortisol immunoassays; hyperandrogenism needs to be monitored with long-term use in women
Mitotane[179,181,187,198]	500 mg to 4 g total per day, orally, up to 5 g in Cushing's disease per day given three times a day	Retrospective studies show approximately 80% UFC normalisation	Gastrointestinal disturbances, dizziness, cognitive alterations, adrenal insufficiency; increased liver enzymes; treatment should be stopped if elevations are >5 × ULN	Approved by the FDA and EMA for treatment of adrenal cancer with endogenous Cushing's syndrome; slow onset of action, highly variable bioavailability; narrow therapeutic window (dose titration based on mitotane plasma concentrations); 11-deoxycortisol can cross-react in cortisol immunoassays; neurological toxicity could be a limiting factor; teratogenicity and abortifacient activity, coupled with a long half-life, could limit use in women who desire future pregnancy
Etomidate[179,199–201]	0·04–0·1 mg/kg/h intravenously for patients in the intensive care unit; 0·025 mg/kg/h for patients not in the intensive care unit	Retrospective studies show approximately 100% serum cortisol control (10–20 µg/dL)	Sedation or anaesthesia; adrenal insufficiency, myoclonus, nausea, vomiting, and dystonic reactions at higher anaesthetic doses	Off-label use only; very rapid onset of action, appropriate for acute treatment of severe hypercortisolism; intravenous hydrocortisone required at high doses to avoid adrenal insufficiency
Levoketoconazole*[202,203]	300–1200 mg total per day, orally, given twice a day	Phase 3 open label study showed 31% UFC normalisation (primary endpoint), 42% normalisation when using imputed data (comparable with other studies); phase 3 randomised withdrawal study showed that 41% lost response with drug *vs* 96% with placebo; clinical signs and symptoms of hypercortisolism improved	Gastrointestinal disturbances, headache, oedema, increased liver enzymes, adrenal insufficiency	Investigational; FDA and EMA orphan drug status for treatment of endogenous Cushing's syndrome; possible lower risk for hepatotoxicity than with ketoconazole based on animal models, although no head-to-head studies in humans available; needs gastric acid for absorption (avoid proton-pump inhibitors); risk of QTc prolongation; careful review of other medications for potential drug–drug interactions is essential
Somatostatin receptor ligands				
Pasireotide[179,187,204–206]	0·6–1·8 mg/mL subcutaneously total per day, given twice a day	Phase 3 study showed 15–26% UFC normalisation	Hyperglycaemia, type 2 diabetes, diarrhoea, nausea, abdominal pain, cholelithiasis, fatigue	Widely approved for patients with Cushing's disease in whom pituitary surgery is not an option or has not been curative; may decrease tumour volume; high risk of hyperglycaemia requires careful patient selection; risk of QTc prolongation
Pasireotide long-acting release[181,207–209]	10–30 mg per month, intramuscularly	Phase 3 study showed 40% UFC normalisation; clinical signs and symptoms of hypercortisolism improved	Hyperglycaemia, type 2 diabetes, diarrhoea, nausea, abdominal pain, cholelithiasis, fatigue	Widely approved for patients with Cushing's disease in whom pituitary surgery is not an option or has not been curative; decreases tumour volume; high risk of hyperglycaemia requires careful patient selection; risk of QTc prolongation

(Table 2 continues on next page)

	Commonly used doses	Efficacy	Adverse effects	Key considerations
(Continued from previous page)				
Dopamine receptor agonists				
Cabergoline[179,187,210–214]	0·5–7 mg total per week, orally	Retrospective studies showed approximately 40% UFC normalisation initially, but roughly 25–40% escape; clinical signs and symptoms of hypercortisolism improved	Headache, nasal congestion, hypotension, depression, dizziness	Off-label use only for Cushing's disease; decreases tumour volume in up to 50% of the patients evaluated; poor response could be due to under-titration; risk of treatment-induced impulse-control disorder; unclear risk for cardiac valvulopathy
Glucocorticoid receptor blocker				
Mifepristone[179,187,215–218]	300–1200 mg total per day orally, given once a day	Open-label phase 3 study showed significant improvement in glycaemia (approximately 60% of patients) and blood pressure; clinical signs and symptoms of hypercortisolism improved	Gastrointestinal disturbances, headache, hypokalaemia, arthralgia, peripheral oedema, hypertension, vaginal bleeding, adrenal insufficiency	FDA-approved for hyperglycaemia associated with Cushing's syndrome; no cortisol markers of efficacy; challenging to use outside specialised clinical practice; risk of hypokalaemia and adrenal insufficiency, needs close monitoring; careful review of other medications for potential drug–drug interactions is essential

EMA=European Medicines Agency. FDA=US Food and Drug Administration. ULN=upper limit of normal. UFC=urinary-free cortisol. *Investigational drug with completed phase 3 clinical trials.

Table 2: **Summary of medical therapies for Cushing's disease**

does not show tumour presence, reoperation might be appropriate if an experienced surgeon at a high-volume centre considers it feasible and positive pathology or a central gradient on IPSS was seen before the initial operation (low quality, discretionary recommendation).

Medical therapy for Cushing's disease

Drugs used for treatment of Cushing's disease target adrenal steroidogenesis, somatostatin and dopamine receptors in the pituitary gland, and glucocorticoid receptors.[6,7,178] Drugs can be used to treat hypercortisolism in patients with persistent or recurrent Cushing's disease and those who are not candidates or refuse surgery, and to control cortisol concentrations in patients undergoing radiotherapy.[139,179,180] Available medications and investigational drugs that have reported phase 3 trial results are described in table 2.

Targeting adrenal steroidogenesis

Adrenal steroidogenesis inhibitors that have been available for many years, including ketoconazole, metyrapone, mitotane, and etomidate, as well as the recently approved osilodrostat, block one or more adrenal enzymes, decreasing glucorticoid synthesis or adrenal androgen production and secretion, or both.[181] They are effective in controlling cortisol excess, but do not directly target the pituitary ACTH-secreting adenoma, nor do they restore HPA-axis circadian rhythm.[182]

When treatment is dose-titrated to achieve cortisol normalisation, there is a risk of adrenal insufficiency with overtreatment. Alternatively, for patients treated from the start with high doses of adrenal steroidogenesis inhibitors to block endogenous cortisol secretion and with exogenous glucocorticoid replacement to avoid adrenal insufficiency (ie, a block-and-replace regimen), there is a risk of inappropriate glucocorticoid over-replacement if blockade is incomplete.[180] Some adverse events relate to ACTH increase in patients with Cushing's disease and buildup of adrenal hormones proximal to the blockade with mineralocorticoid or androgenic activity. Potential adverse events related to drug–drug interactions are a key factor in treatment selection and use.[183]

Ketoconazole

Ketoconazole blocks multiple adrenal enzymes, including those involved early in the steroid biosynthetic pathway. This approach avoids excess circulation of androgen and mineralocorticoid precursors, but it can also decrease gonadal steroid synthesis; men might experience hypogonadism and gynecomastia, which can limit prolonged treatment.[184] A review of 310 patients with Cushing's syndrome treated in five studies with a mean dose of 673·9 mg per day of ketoconazole and followed for a mean of 12·6 months showed UFC normalisation in 64·3% of patients (median 50%, range 44·7–92·9%), but up to 23% of initially responsive patients lost biochemical control.[179] Similarly, data derived from the largest retrospective study of 200 patients with Cushing's disease who took ketoconazole showed that 33 (64·7%) of 51 patients treated for more than 24 months with a mean dose of 600 mg per day normalised UFC concentrations, but 15·4% escaped.[185] Improvement in clinical features of Cushing's syndrome has also been observed, including decreased bodyweight and blood pressure, improved glucose metabolism, and decreased muscle weakness.[179]

Hepatotoxicity (10–20% of patients) is mostly asymptomatic with mild or moderate increases in liver enzymes (≤5×ULN),[186] and typically appears within the first 6 months of treatment; these increases seem not to be dose-dependent and reverse within 2–12 weeks after dose decrease or discontinuation. However, because serious hepatotoxicity has been reported in patients without obvious risk factors, the United States Food and Drug Administration (FDA) introduced a black-box

warning and recommends weekly monitoring of liver function tests in patients with fungal infections treated with ketoconazole. Of note, ketoconazole use for Cushing's syndrome is off-label in the USA. Gastrointestinal disturbances and adrenal insufficiency are also common, seen in 5–20% of patients, and skin rash is observed in approximately 5%.[179] There are several drug–drug interactions with ketoconazole; careful review of the patient's medication list for potentially problematic interactions is essential.

Metyrapone

Treatment with the 11β-hydroxylase inhibitor metyrapone in 120 patients with Cushing's syndrome (five studies; mean dose 2127·5 mg per day, mean follow-up 8·7 months) showed UFC normalisation in 71% (median 75·5%; range 45·4–100%), with up to 18% escaping after initial response.[179] A subsequent retrospective multicentre study of 164 patients with Cushing's syndrome reported that 43% achieved biochemical control with UFC, with a mean of 8 months monotherapy, at a mean starting dose of 1040 mg per day and escalating to 1425 mg per day.[193] An observational study of 31 patients with Cushing's syndrome, including 20 with Cushing's disease, showed that a median dose of 1000 mg per day for 9 months induced a rapid decrease from baseline in both UFC (–67%) and LNSC (–57%) after the first month of treatment, with sustained normalisation in UFC in 70% of patients and in LNSC in 37% of patients at last visit.[194] Three patients had loss of control at 9 months despite normal UFC concentrations at 6 months and two patients also showed normal LNSC. Notably, 11-deoxycortisol might produce clinically relevant cross-reactivity with cortisol in both blood and urine immunoassays.[195] A multicentre prospective study of 50 patients with Cushing's syndrome showed that 23 (47%) had UFC normalisation at 12 weeks (final median metyrapone dose at week 12 was 1500 mg [250; 5500] mg per day) and adrenal insufficiency was reported in 6 (12%) of patients.[196]

Patients treated with metyrapone typically show a general improvement in clinical features of Cushing's syndrome (66% in the prospective study), such as blood pressure, glucose metabolism, psychiatric disturbances, and muscle weakness.[179,196]

Hirsutism, dizziness, arthralgia, fatigue, hypokalaemia, and nausea are the most commonly reported adverse events with metyrapone; adrenal insufficiency, abdominal pain, and atopic dermatitis are less frequently reported.[179] Adverse events secondary to hyperandrogenism can limit prolonged treatment, especially in female patients.

Osilodrostat

Proof-of-concept and phase 2 prospective studies showed that osilodrostat, an 11β-hydroxylase and aldosterone synthase inhibitor, was effective in reducing cortisol and was well-tolerated.[188–190] This drug was further evaluated in 137 patients with Cushing's disease enrolled in a phase 3, prospective, multicentre, double-blind, randomised withdrawal study.[191] After 12 weeks of open-label dose-titrated treatment and 12 additional weeks of open-label dose-optimised treatment, 72 (53%) patients had maintained normal UFC and were eligible for randomisation. By week 34, at the end of the randomised treatment period, 31 (86%) of 36 randomly assigned to osilodrostat maintained normal UFC versus 10 (29%) of 35 randomly assigned to placebo (OR 13·7, 95% CI 3·7–53·4; p<0·0001).

Treatment with osilodrostat also yielded clinical improvements. By week 48, patients showed decreases in bodyweight, blood pressure, total cholesterol, and LDL cholesterol compared with baseline, and decreased fasting serum glucose and HbA_{1c} concentrations. Quality of life and depression scores also improved.[191]

Nausea, anaemia, and headache were reported in 8–11% of patients, and adverse events related to hypocortisolism were reported in about half of patients, mostly during the open-label dose-titration period. These adverse events were generally manageable with dose reductions or interruptions, although glucocorticoid replacement was required in 25 (36%) of 70 patients with one or more hypocortisolism-related adverse events. Additionally, 58 (42%) of 137 treated patients in the phase 3 study showed effects from increased levels of adrenal steroid precursors, including hypokalaemia and hypertension; 12 (11%) of 106 women reported hirsutism.[191] In another prospective phase 3 study of 44 patients, a significantly greater proportion of patients receiving osilodrostat (77%) achieved mean UFC below or equal to the ULN after 12 weeks of treatment versus placebo (8%), with improvements seen in clinical features, cardiovascular disease markers, and quality of life. Hypocortisolism-related adverse events occurred in 27% of patients.[192]

Mitotane

Mitotane inhibits several steroidogenic enzymes and has a long-lasting adrenolytic action in steroid-secreting adrenocortical cells. It suppresses hypercortisolism in 80% of cases, but with a slow onset of action and highly variable bioavailability.[180,198] Induction of CYP3A4-mediated rapid inactivation of cortisol leads to a requirement for a 2–3-times increased glucocorticoid replacement dose when treatment of adrenal insufficiency is needed, or with a block-and-replace strategy.[187] It is rarely used for Cushing's disease. Most workshop participants considered that use of mitotane should be limited to patients with adrenal carcinoma.

Etomidate

Originally developed as an anaesthetic, etomidate was shown to rapidly normalise cortisol concentrations, leading to use for acute control of severe hypercortisolism in patients treated in an intensive care setting.[199] Low-dose

etomidate (0·04–0·05 mg/kg/h) produces partial blockade; a high dose (0·5–1 mg/kg/h) provides for complete blockade, with intravenous hydrocortisone used to avoid etomidate-induced adrenal insufficiency.[200] Very low doses (0·025 mg/kg/h) can be used in patients treated in hospital outside of intensive care,[201] although this might depend on local practice.

Compared with the lipid formulation, the propylene glycol preparation of etomidate is more frequently associated with thrombophlebitis and pain on injection, and also with additional adverse events, such as haemolysis and renal tubular injury, as well as lactic acidosis at high doses.[200]

Targeting pituitary somatostatin and dopamine receptors

Both the dopamine agonist cabergoline and the somatostatin receptor ligand pasireotide are used in patients with Cushing's disease who have persistent or recurrent hypercortisolism,[7,139,179] although only pasireotide is approved by regulatory agencies for use in this population.[7,204,205] Tumour control (shrinkage and growth prevention), which may be seen, is clinically important for patients with a large residual tumour and for patients with corticotroph tumour progression, or Nelson's syndrome.

Pasireotide

In a phase 3 study of 162 patients with Cushing's disease treated with subcutaneous pasireotide, UFC normalised at month 6 in 15–26% of those without dose increases. Higher rates of UFC normalisation were seen in patients with baseline UFC less than five times ULN[204] and significant clinical improvement was noted in most patients.[205]

Another phase 3 study treated 150 patients with Cushing's disease with 10 mg or 30 mg monthly intramuscular pasireotide long-acting release (LAR). At month 7, 62 (40%) patients in both groups showed normalised UFC, regardless of dose titration, with highest response in those with baseline UFC less than two times ULN.[207] At month 12, improvements in blood pressure were greater in those with normalised UFC than in those without normalised UFC; BMI, weight, waist circumference, and quality of life were all improved regardless of UFC control.[208] Long-term extension studies showed that biochemical and clinical improvements could be maintained for up to 5 years in select patients who continued the study.[209,210] Of note, in real-life settings, few data are available about long-term treatment compliance, and several studies show a high rate of treatment discontinuation. Treatment with pasireotide LAR also decreased median tumour volume by 17·8% with the 10 mg dose and 16·3% with the 30 mg dose. 15 (43%) patients who received the 10 mg dose and 18 (47%) who received the 30 mg dose had at least a 20% reduction in median tumour volume.[207]

A longitudinal study in five patients with Cushing's disease with Nelson's syndrome after bilateral adrenalectomy showed that pasireotide LAR rapidly suppressed ACTH concentrations and yielded sustained reductions over 24 weeks.[219]

Between a third and two-thirds of Cushing's disease tumours harbour a mutation in *USP8*,[220,221] and these mutated tumours can show higher SST5 expression compared with wild-type tumours.[222,223] Because pasireotide has a high affinity for this receptor, *USP8* mutational status might prove to be a useful marker for predicting treatment response.

The risk for hyperglycaemia is high with pasireotide.[204,205,224–226] In the two phase 3 studies,[204,207] approximately 70% of patients reported hyperglycaemia-related adverse events, with new antidiabetic medication initiation or dose adjustments required in approximately half of patients. The high rates of hyperglycaemia are thought to result from inhibition of insulin and incretin secretion combined with a lesser degree of glucagon inhibition.[215] Management with GLP-1 receptor agonists or DDP-4 inhibitors is therefore thought to be useful.[226,227]

Cabergoline

Available data on cabergoline use in Cushing's disease are derived mostly from small retrospective studies demonstrating biochemical normalisation in 25–40% of patients, with loss of control in 20–40% of patients who are initially normalised.[210,211]

A retrospective, multicentre cohort study of 53 patients treated with a median cabergoline dose of 2·3 mg per week (range 0·5–6·0) yielded normal UFC in 40% of patients during the first year, but only 23% of those showed sustained UFC normalisation after a median 32·5 months follow-up.[212] The low control rate could be due to under-titration, as a smaller study of 20 patients on cabergoline titrated to maximum of 7 mg per week (median 3·5 mg per week) showed normalised UFC in eight (40%) of patients at 24 months.[213] Weight, glycaemic control, and hypertension improved in 25–40% of complete responders,[212] and tumour shrinkage was reported in 50%.[213] Patients with Nelson's syndrome can also respond to cabergoline, and both ACTH normalisation and tumour shrinkage have been reported.[228] Although not approved in this setting, cabergoline has been used in pregnant patients with prolactinomas and other pituitary adenomas, including Cushing's disease.[179]

Cabergoline-induced impulse-control disorder is probably under-reported, and can manifest as hypersexuality, pathological gambling, excessive alcohol consumption, overeating, and uncontrolled shopping.[214] This behaviour can occur within months of initiating cabergoline therapy, or might manifest later, and improves or resolves after treatment discontinuation.[229,230]

High cumulative doses of ergotamine-derived dopamine agonists used in patients with Parkinson's disease were associated with risk of cardiac valve

regurgitation.[231] Although one study in prolactinomas found that moderate tricuspid regurgitation was more frequent with higher doses,[232] a large multicentre study found no association between the cumulative cabergoline dose and age-corrected prevalence of any valvular abnormality.[233] Furthermore, a meta-analysis showed that

Panel 3: Medical therapy for Cushing's disease

Which factors are helpful in selection of a medical therapy?

- If there is a need for rapid normalisation of cortisol, we recommend an adrenal steroidogenesis inhibitor; osilodrostat and metyrapone have the fastest action and are orally available, while etomidate can be used intravenously in very severe cases (high quality, strong recommendation)
- In mild disease, if residual tumour is present and there is a potential for tumour shrinkage, consider pasireotide or cabergoline (moderate quality, strong recommendation)
- If there is a history of bipolar or impulse control disorder, consider avoiding cabergoline (moderate quality, strong recommendation)
- If an expert pituitary endocrinologist is not available to monitor treatment response, use mifepristone cautiously (low quality, discretionary recommendation); we recommend counselling patients that cortisol cannot be used to monitor treatment response or adrenal insufficiency (high quality, strong recommendation). Drug–drug interactions must be considered when this medication is used
- In pregnant women or those desiring pregnancy, consider cabergoline or metyrapone (low quality, discretionary recommendation), although no Cushing's disease medications are approved for use in pregnancy
- Drug intolerance or side-effects, as well as concomitant comorbidities such as type 2 diabetes and hypertension, should further guide type of medication used (moderate quality, strong recommendation)
- Consider cost and estimated therapy duration, especially if definitive treatment (ie, pituitary or adrenal surgery) is planned or while awaiting effects of radiotherapy (low quality, discretionary recommendation)

Which factors are used in selecting an adrenal steroidogenesis inhibitor?

- Rapidity of action, tolerability, ease-of-use, degree of probable biochemical normalisation, and specific clinical improvement, as well as local availability and cost of each drug, should be considered at therapy start (moderate quality, strong recommendation)
- Ketoconazole might be favoured for ease of dose titration; concern about inducing hepatotoxicity and the need to monitor liver enzymes can lead to under-dosing (moderate quality, strong recommendation). Drug–drug interactions must be considered and hypogonadism may occur in men
- Osilodrostat achieves high rates of cortisol normalisation. Dosing schedule might be more convenient for patients than with metyrapone, but neither metyrapone nor osilodrostat is limited by hypogonadism in men (high quality, strong recommendation)
- Mitotane is rarely used as monotherapy in Cushing's disease in most centres (low quality, discretionary recommendation)

How is tumour growth monitored when using an adrenal steroidogenesis inhibitor or glucocorticoid receptor blocker?

- MRI is typically obtained 6–12 months after initiating treatment and repeated every few years depending on the clinical scenario (moderate quality, strong recommendation)
- It can be difficult to determine whether tumour progression is due to loss of cortisol feedback or reflects the underlying behaviour of aggressive, recurrent disease (low quality, discretionary recommendation)
- We suggest monitoring ACTH concentrations, because progressive elevations in ACTH could be a sign of tumour growth and a need for MRI; although the half-life of ACTH is short, concentrations fluctuate, and they do not necessarily reflect tumour growth (low quality, discretionary recommendation)
- If progressive tumour growth is seen, medical treatment should be suspended and the management plan reassessed (moderate quality, strong recommendation)

When is preoperative medical therapy used?

- There are no rigorous data supporting use of preoperative medical therapy (moderate quality, strong recommendation)
- Most experts would consider use of adrenal steroidogenesis inhibitors if surgery is delayed, either because of scheduling or because of external factors (low quality, discretionary recommendation)
- Patients with severe Cushing's disease who have potentially life-threatening metabolic, psychiatric, infectious, or cardiovascular or thromboembolic complications might benefit from preoperative medical therapy in select cases (low quality, discretionary recommendation)

How is treatment response monitored? Which factors are considered in deciding whether to use combination therapy or to switch to another therapy?

- Response should be defined on the basis of a combination of clinical endpoints (eg, improved phenotype, weight, hypertension, glucose metabolism, quality of life) and biochemical endpoints, or only clinical endpoints when glucocorticoid receptor blockers are used (moderate quality, strong recommendation)
- Cortisol concentrations are often measured by urinary free cortisol (except when using mifepristone); urinary free cortisol is not useful if adrenal insufficiency is a concern and morning serum cortisol is preferred (high quality, strong recommendation)
- Because of the loss of biological circadian rhythm, it is unclear whether targeting diurnal secretion alone with morning cortisol or with late-night salivary cortisol is meaningful (low quality, discretionary recommendation)

(Panel 3 continues on next page)

(Continued from previous page)

- Change in treatment should be considered if cortisol levels are persistently elevated after 2–3 months on maximum tolerated doses (moderate quality, strong recommendation)
- If cortisol does not normalise but is reduced or there is some clinical improvement, combination therapy can be considered (low quality, discretionary recommendation)
- If there is clear resistance to treatment despite dose escalation, we suggest switching to a different therapy (low quality, discretionary recommendation)

Which drugs are used for optimal combination therapy?

- There are few rigorous data supporting specific regimens for combination therapy (high quality, strong recommendation)
- Many experts consider combining ketoconazole with metyrapone or potentially ketoconazole with osilodrostat to maximise adrenal blockade when monotherapy is not effective, or to allow lower doses of both drugs (low quality, discretionary recommendation)
- Ketoconazole plus cabergoline or pasireotide, and pasireotide plus cabergoline could be rational combinations if there is visible tumour present (low quality, discretionary recommendation)
- Other combinations that can be used include triplets of cabergoline, pasireotide, plus ketoconazole, and ketoconazole, metyrapone, plus mitotane (low quality, discretionary recommendation)

it remains an open question whether such echocardiographic findings are clinically significant.[234]

Targeting the peripheral tissue glucocorticoid receptor

Mifepristone

The glucocorticoid receptor blocker mifepristone is effective in controlling some effects of hypercortisolism, regardless of the cause.

An open-label study of 50 patients with endogenous Cushing's syndrome, including 43 with Cushing's disease, showed that after 24 weeks of treatment, 15 (60%) of 25 patients with a concurrent diagnosis of type 2 diabetes or impaired glucose tolerance had a significant reduction of at least 25% from baseline in area under the curve for glucose during an oral glucose tolerance test, and eight (38%) of 21 patients with hypertension showed a significant reduction of at least 5 mm Hg in diastolic blood pressure. Insulin resistance, weight, waist circumference, and quality of life also improved.[215]

Twelve patients had increased blood pressure, including nine with hypokalaemia who required spironolactone, consistent with mineralocorticoid receptor activation. Endometrial hypertrophy and irregular menstrual bleeding were also reported, consistent with the antiprogesterone activity of mifepristone. Dexamethasone was administered in seven patients with signs and symptoms of adrenal insufficiency, underscoring the need for careful monitoring.[215] Cortisol concentrations remain high despite treatment with mifepristone, and measures of low cortisol typically used to confirm adrenal insufficiency due to overtreatment with other medical therapies cannot be used with mifepristone. Rather, only clinical features can be used.[216]

Continued mifepristone treatment of 27 patients with Cushing's disease included in a long-term extension study showed sustained increases in ACTH concentrations of at least two times, but tumour volume progression, seen in three patients with macroadenomas up to 25 months from baseline, did not correlate with ACTH increases.[217] Thyroid function should be closely monitored and thyroid hormone replacement adjusted as needed.[218] All concomitant medications should be carefully reviewed given the potential for drug–drug interactions with mifepristone.

Clinical considerations and recommendations for medical therapy

We recommend individualising medical therapy for all patients with Cushing's disease based on the clinical scenario, including severity of hypercortisolism. Regulatory approvals, treatment availability, and drug costs vary between countries and often influence treatment selection. However, where possible, it is important to consider balancing cost of treatment with the cost and the adverse consequences of ineffective or insufficient treatment. In patients with severe disease, the primary goal is to treat aggressively to normalise cortisol concentrations (or cortisol action if using mifepristone). Multiple serial tests of both UFC and LNSC are used to monitor treatment outcomes.[158,235,236]

A brief summary of workshop discussions about how to best incorporate each of the different treatment options is presented in panel 3 and in figure 2.

Initial treatment selection for medical therapy

Adrenal steroidogenesis inhibitors are usually used first given their reliable effectiveness. For patients with mild disease and no visible tumour on MRI, ketoconazole, osilodrostat, or metyrapone are typically preferred. Cabergoline can also be used for mild Cushing's disease; it is less effective and has a slower onset of action, but requires less frequent dosing than the drugs previously described. For patients with mild-to-moderate disease and some residual tumour, there might be a preference for cabergoline or pasireotide because of the potential for tumour shrinkage. However, the high rate of hyperglycaemia with pasireotide would make patient selection crucial.

For patients with severe disease, rapid normalisation of cortisol is the most important goal. With osilodrostat and metyrapone, response will typically be seen within hours, and with ketoconazole within a few days. Intravenous etomidate also works rapidly and could be used if the patient cannot take oral medications. For patients with severe hypercortisolism, combinations of steroidogenesis inhibitors might be necessary. However, if hypercortisolism is severe and not responsive to optimised medical therapy, including combinations, bilateral adrenalectomy should be considered to avoid worsening outcomes.

Other patient factors can be important for initial treatment selection. For example, cabergoline should not be used in patients with a history of bipolar or impulse control disorder, but might be preferred in a young woman desiring pregnancy. Although none of these drugs are specifically approved for use in pregnancy, metyrapone might be considered with precautions in selected women who are pregnant. In such cases, given the higher normal cortisol levels during pregnancy, a higher cut-off target for cortisol (eg, 1·5×ULN) is used.

Mifepristone improves key clinical features associated with hypercortisolism, specifically hyperglycaemia and weight gain. However, it could be challenging to use in standard clinical practice, and often worsens hypokalaemia. There are no reliable biochemical markers for monitoring cortisol concentrations, increasing the risk of adrenal insufficiency due to overtreatment, and the long

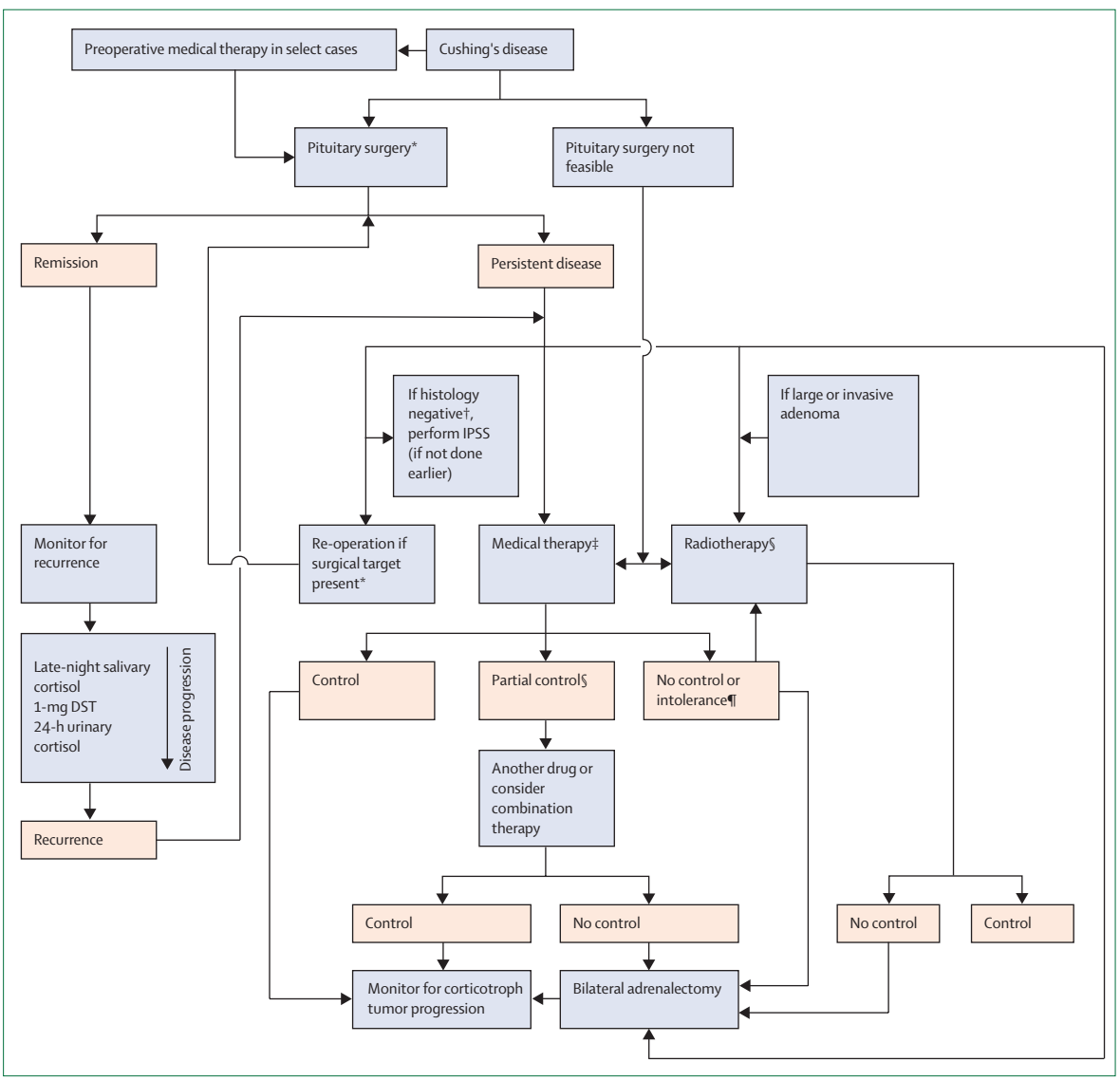

Figure 2: **Algorithm for management of Cushing's disease**
DST=dexamethasone suppression test. IPSS=inferior petrosal sinus sampling. ACTH=adrenocorticotropic hormone. *Pituitary surgery should be performed by an experienced surgeon. †Absence of ACTH-staining adenoma. ‡See table 2 and panel 3 for considerations regarding selection of medical therapy. §Lifelong monitoring for hypopituitarism and secondary neoplasia in the radiation field required. ¶On maximum tolerated dose of the drug.

half-life of mifepristone and its metabolite requires several days of stress-dose glucocorticoid replacement, preferably dexamethasone, if adrenal insufficiency ensues. Because cortisol measurements are not helpful for dosing or safety monitoring, mifepristone should be used only by clinicians with extensive experience in Cushing's disease; it is also important to counsel patients that monitoring cortisol concentrations is not reliable, especially for adrenal insufficiency.

There are few rigorous data supporting specific regimens for combination therapy, but several have been described.[197,237,238] Many experts consider combining ketoconazole with metyrapone to maximise adrenal blockade when monotherapy is not effective or to allow lower doses of both drugs, although a steroidogenesis inhibitor plus a tumour-targeting agent, such as ketoconazole plus cabergoline, is also a rational combination, especially if visible tumour is present. Other combinations that could be used include triplets of cabergoline, pasireotide, plus ketoconazole; and metyrapone, ketoconazole, plus mitotane. Risk of potentiating adverse effects with combination therapy, such as QTc prolongation, should also be considered.

Selecting an adrenal steroidogenesis inhibitor

The longest clinical experience for adrenal steroidogenesis inhibitors is with ketoconazole and metyrapone. These agents are approved for use in Cushing's disease in Europe by the EMA, but not in the USA (where only osilodrostat is approved in this category by the FDA), and they might not be available in some countries. Ketoconazole might be favoured for ease of dose titration, but it is often under-dosed for fear of inducing hepatotoxicity. Liver function tests should be regularly monitored, but treatment does not necessarily have to be discontinued if liver function tests are mildly elevated, yet stable.[239] Osilodrostat and metyrapone can induce rapid control in the majority of patients. They are not limited by monitoring of liver function tests and hypogonadism does not occur in men. It is expected that osilodrostat will be increasingly used as it becomes widely available given its high efficacy and twice-daily dosing. It is necessary to monitor for adrenal insufficiency and osilodrostat effects on androgens, but whether treatment selection should be based on patient sex in long-term treatment is not yet known. Mitotane, rarely used for patients with Cushing's disease in most centres, has a slower onset of action.

A block-and-replace regimen could be considered for patients with severe disease or cyclical Cushing's syndrome, and in patients ineligible for surgery. This might be a particularly useful approach if monitoring visits are infrequent because of external factors such as the COVID-19 pandemic, lack of transportation, or other issues. Caution is needed to avoid glucocorticoid over-replacement and inducing iatrogenic Cushing's syndrome.

Monitoring response to medical therapy

For all patients, regular monitoring for treatment efficacy is required, including measures of cortisol (except with mifepristone) and patient symptoms and comorbidities, especially weight, glycaemia, and blood pressure. In addition, quality of life is important to take into account, preferably through patient-reported outcomes. Cortisol concentrations are often measured by UFC; notably, this test is not useful for diagnosis of adrenal insufficiency. Morning cortisol, LNSC, or both could be used as an alternative, but because of the loss of circadian rhythm, it is unclear whether targeting diurnal secretion alone is meaningful. Nevertheless, morning cortisol values might be especially pertinent in patients taking higher medication doses in the evening than in the morning.[182] Patients who normalised both UFC and LNSC with pasireotide LAR had better clinical outcomes than those who normalised UFC alone,[235] and a higher treatment dose at bedtime for twice daily medications might help restore circadian rhythm patterns, but there is no rigorous evidence to support the latter approach.

As designs, medication up-titration schemes, comparator arms, inclusion and exclusion criteria, and primary endpoints differ even among prospective studies, it is difficult to directly compare treatment outcomes, either for efficacy or for adverse effects. Furthermore, some drugs have not been prospectively studied for Cushing's syndrome. When using UFC normalisation as a target, osilodrostat has the highest efficacy on the basis of data from several prospective clinical trials, followed by metyrapone (retrospective and prospective data), ketoconazole (retrospective data), pasireotide (prospective data), and cabergoline (retrospective and prospective data). Because improvement in clinical features of Cushing's syndrome and diabetes are used as markers of mifepristone efficacy, this drug cannot be directly compared for biochemical efficacy with other available treatments.

Change in treatment should be considered if cortisol concentrations are persistently elevated after 2–3 months on maximum tolerated doses. If cortisol does not normalise but is reduced or there is some clinical improvement, combination therapy can be considered. If there is clear resistance to treatment, we suggest switching to a different therapy. However, it is important to ensure that insufficient disease control due to under-dosing is not misinterpreted as treatment resistance.

With adrenal-targeting agents, there can be concern for tumour growth due to ACTH-cortisol feedback interruption. However, it can be difficult to determine whether such tumour progression is due to this loss of feedback or reflects the underlying behaviour of aggressive, recurrent disease. We suggest monitoring ACTH concentrations, as substantial increases could portend new tumour growth and a need for MRI, with the caveats that ACTH has a short half-life and concentrations fluctuate, and so they might not necessarily reflect tumour growth. If progressive increase in tumour size is noted,[240] treatment should be

suspended and management reassessed. MRI is typically done 6–12 months after initiating treatment and repeated every few years, depending on the clinical scenario.

With combination therapies, it is also important to monitor for potential overlapping toxicities, particularly QTc prolongation, as well as drug–drug interactions.

Primary and preoperative medical therapy for de novo Cushing's disease

Primary medical therapy is used when successful adenoma resection is unlikely because of unfavourable localisation, clinically significant invasiveness, or lack of visualisation on MRI. Double-blind, randomised phase 3 studies evaluating the efficacy of several novel drugs included a small proportion of patients with de novo Cushing's disease, ranging from 0% to 28%.[187] Further studies are needed to demonstrate utility of the different medical therapies in this setting, either as monotherapy or in combination, while also taking into account the potential effects of such treatment on adenoma size.

Published evidence regarding preoperative medical therapy in patients with Cushing's disease is sparse, and it is not used in most patients, although there are regional variations. A meta-analysis showed no differences in cortisol normalisation rate between participants who received cortisol-lowering medications in the preoperative setting versus later use as adjuvant treatment.[241] Preoperative medical therapy could be an option in severely ill patients for whom surgery is contraindicated or if waiting time for surgery is long,[139] or in patients with life-threatening complications of hypercortisolism requiring rapid cortisol control.[242] Physician surveys show that preoperative therapy, mostly with ketoconazole or metyrapone, is used in up to 20% of patients with Cushing's disease, especially those with more severe clinical features or nonvisible adenoma.[243]

Retrospective studies show that therapy with preoperative steroidogenesis inhibitors for a mean of 4 months yields cortisol normalisation rates of 50–72%, although subjective symptom improvement was observed in only a third of cases.[185,193] Lower rates of postoperative hypoadrenalism from preoperative medical therapy could, in theory, protect against the occurrence of a proinflammatory and procoagulant state,[94,243] but postsurgical complications, including VTE, are similar regardless of its use.[243] If the HPA axis recovers during preoperative treatment, adrenal insufficiency might not occur postoperatively, so it can be more difficult to determine whether remission is present.

Preoperative cabergoline probably has limited value, because a substantial decrease in cortisol was seen in only a quarter of patients in a cohort treated prospectively for 6 weeks.[244]

Clinical considerations and recommendations for primary and preoperative medical therapy for de novo Cushing's disease

There are no rigorous data supporting use of primary or preoperative medical therapy. Most experts would consider such an approach with adrenal steroidogenesis inhibitors if surgery is delayed, either because of scheduling or due to external factors such as a pandemic (very low quality, discretionary recommendation).

Patients with severe Cushing's disease who have potentially life-threatening metabolic, psychiatric, infectious, or cardiovascular or thromboembolic complications might also benefit from preoperative medical therapy in select cases (low quality, discretionary recommendation). Although this benefit has not been clearly confirmed, some experts consider it might have a potentially favourable effect on glucose, cardiovascular, and coagulation parameters (very low quality, discretionary recommendation). Few experts use it to decrease the extent of postoperative cortisol withdrawal manifestations.

Monitoring and follow-up of patients treated with preoperative therapy can be challenging because postoperative cortisol assessments for surgical cure are not reliable. The patient's perspective regarding this approach would be valuable to incorporate into future research studies (very low quality, discretionary recommendation).

Radiotherapy

Radiotherapy is primarily used as adjuvant therapy for patients with persistent or recurrent disease after transsphenoidal surgery[7,245] or for aggressive tumour growth. Approximately two-thirds of patients achieve biochemical remission during the years after treatment with conventional external-beam radiotherapy, typically 45–50 Gy administered in less than 2 Gy fractions, or stereotactic radiosurgery, which is administered as single dose or a few fractions of approximately 20 Gy.[246] However, more recent series with stereotactic radiosurgery, including whole sellar radiotherapy,[247] show higher biochemical remission rates. In a multicentre study of GammaKnife stereotactic radiosurgery in 278 participants followed for a mean of 5·6 years, biochemical control was attained in 193 (80%) and durable hypercortisolism control was maintained in 158 (57%).[248] Tumour control rates are typically higher, with approximately 95% of patients treated with stereotactic radiosurgery showing decreased or stable tumour volume as observed on MRI.[246] A small single-centre study of proton-beam radiotherapy showed complete response (either cortisol or ACTH normalisation) in patients with persistent corticotroph adenomas due to Cushing's disease or Nelson's syndrome, with low morbidity after a median follow-up of 62 months.[249]

Stereotactic radiosurgery can also be used as primary therapy in patients with high surgical risk or who refuse surgery. In this setting, endocrine remission was attained in 17 (81%) of 21 patients with Cushing's disease at 5 years of follow-up.[250] Long-term follow-up is needed as recurrence and tumour growth have been described post-radiotherapy.

Given the latency until post-radiotherapy remission, adjuvant medical therapy is needed to control hypercortisolism; periodic withdrawal allows evaluation of

cortisol secretion to assess treatment effect.[7] Although data are mixed on whether ketoconazole[248,251] or cabergoline[252] treatment at the time of stereotactic radiosurgery limits efficacy, they are often withheld temporarily at the time of radiotherapy.

Hypopituitarism is the most common side-effect of both conventional radiotherapy and stereotactic radiosurgery, seen in 25–50% of patients, and generally increases over time. Risk of secondary malignancy, cranial nerve damage, and stroke are low with stereotactic radiosurgery.[253] In patients treated with stereotactic radiosurgery, a distance of at least 3–5 mm between the tumour and the optic chiasm and a chiasm dose less than 8 Gy is recommended to limit treatment damage.[253] Long-term data will help address whether use of different stereotactic radiosurgery modalities (eg, GammaKnife, linear accelerator, proton beam) confers lower rates of stroke and hypopituitarism compared with conventional radiotherapy.[254]

Clinical considerations and recommendations for radiotherapy

Radiotherapy is most commonly used in cases of persistent hypercortisolism after incomplete corticotroph tumour resection, particularly if the tumour is aggressive or invasive or is considered unresectable (high quality, strong recommendation). Stereotactic radiosurgery is probably more convenient as few treatment sessions are required, but avoiding optic chiasm exposure is crucial (high quality, strong recommendation). Lifelong monitoring for pituitary hormone deficiencies and recurrence is required in all patients undergoing radiotherapy (high quality, strong recommendation). Imaging for secondary neoplasia in the radiation field should also be considered (high quality, strong recommendation).

Adrenalectomy

Bilateral adrenalectomy offers immediate control of cortisol excess in patients with persistent or recurrent Cushing's disease that is not responsive to medical therapy,[7,139,255] but it is only considered for selected patients because of the resultant adrenal insufficiency and need for life-long glucocorticoid and mineralocorticoid replacement therapy.[256] Laparoscopic bilateral adrenalectomy using either a transperitoneal or posterior retroperitoneal approach was associated with a 10–18% complication rate and a mortality rate of less than 1% in the largest series.[257,258] Long-term clinical relapse of hypercortisolism due to adrenal rest stimulation by high ACTH is uncommon (<10%), whereas clinical improvement in BMI, type 2 diabetes, hypertension, and muscle weakness has been reported in more than 80% of patients.[259]

Corticotroph tumour progression after bilateral adrenalectomy is a long-term concern in 25–40% of patients after 5–10 years.[259–261] Most cases can be managed with surgery, radiotherapy, or medical therapy. However, a subset of aggressive tumours will continue to grow and long-term monitoring is required. A European consensus focused on management of these patients was published in 2021.[262]

Corticotroph tumour progression after bilateral adrenalectomy does not seem to be influenced by pregnancy.[263] This might make bilateral adrenalectomy a preferred option in female patients with an immediate pregnancy plan. In most cases, however, bilateral adrenalectomy is rarely performed as the first-line treatment after failure of initial pituitary surgery, and duration of disease before adrenal surgery is typically 3–4 years or longer.[258] Whether and how this might affect long-term treatment outcomes remains unknown.

Clinical considerations and recommendations for adrenalectomy

In patients with Cushing's disease, bilateral adrenalectomy is often considered to be a treatment of last resort in most centres after all other options have failed (moderate quality, strong recommendation). However, bilateral adrenalectomy can be warranted earlier in patients with severe hypercortisolism in whom a rapid, definitive effect on cortisol is needed to avoid prolonged systemic effects of uncontrolled disease (moderate quality, strong recommendation). Many expert centres recommend bilateral adrenalectomy earlier in the course of the disease for female patients with Cushing's disease desiring pregnancy (moderate quality, strong recommendation).

After bilateral adrenalectomy, plasma ACTH and serial pituitary imaging are used for monitoring at intervals dictated by the clinical scenario, usually starting 6 months after surgery (high quality, strong recommendation). More frequent evaluation might be necessary if there is a clinical suspicion of corticotroph tumour progression (high quality, strong recommendation).

Additional considerations

Genetics of Cushing's disease

Corticotroph adenomas are predominantly of sporadic origin, based on a monoclonal expansion of a singular mutated cell.[264] These adenomas abundantly express EGFR, which signals to induce ACTH production.[265] Somatic activating driver mutations in *USP8* are present in 36–60% of corticotroph adenomas.[211] These mutations lead to persistent overexpression of EGFR, thereby perpetuating the hyper-synthesis of ACTH. Rarely, mutations in the glucocorticoid receptor *NR3C1*, the *BRAF* oncogene, the deubiquitinase *USP48*, and *TP53* are encountered.[264] Patients with familial tumour syndromes, such as *MEN1*, *FIPA*, and *DICER1*, rarely develop corticotroph adenomas. It has been proposed that corticotroph tumours could be sub-classified on the basis of *USP8* driver mutations and clinical behaviour.[266] As *USP8* mutational status might predict recurrence after transsphenoidal surgery,[267] such genomic classifications could open new avenues for more targeted, personalised treatment modalities in the future.

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Diagnosis and management of Cushing's syndrome in children

Endogenous Cushing's syndrome is very rare before age 18 years. Germline mutations in *MEN1, RET, AIP, PRKAR1A, CDKN1B, DICER1, CABLES1,* and *SDH*-related genes can all predispose children to Cushing's disease, although screening is usually reserved for cases in which there is either family history or other signs suggestive of a genetic syndrome.[268]

Lack of height increase concomitant with weight gain is the most common Cushing's syndrome presentation in children, making the disorder somewhat easier to detect than in post-pubertal adolescents or adults. Using the insulin tolerance or glucagon stimulation test, prevalence of severe growth hormone deficiency (<9 mU/L) is estimated at 31% and partial growth hormone deficiency (<30 mU/L) is estimated at 54%.[269]

Documentation of hypercortisolism with 24-h UFC, LNSC, or overnight 1 mg DST are all used to confirm diagnosis. The diagnostic approach and test performances are slightly different from adults, as recently extensively reviewed.[270] The Dex-CRH test is not useful in children. In children older than 6 years, Cushing's disease is the most common cause of Cushing's syndrome, whereas adrenal causes are more common in younger children. There are algorithms for testing to distinguish ACTH-dependent from ACTH-independent Cushing's syndrome. Notably, the role of IPSS in children is more limited than in adults.[271]

As in adults, surgical resection of the ACTH-secreting tumour is the first-line treatment in children. However, unlike in adults, thromboprophylaxis should not be routinely used because of bleeding risk, but is reserved for selected paediatric patients. With successful treatment, adrenal function typically recovers within approximately 12 months.[272] Evaluation for growth hormone deficiency should be done by 3–6 months postoperatively, and immediate growth hormone replacement given if needed to ensure proper growth; growth hormone replacement ensures adequate final height, but obesity is not fully reversible.[273] For paediatric patients requiring medical therapy, ketoconazole or metyrapone is typically used with morning cortisol for monitoring response. Pasireotide is not recommended and clinical trials of osilodrostat in children are underway. Block-and-replace regimens with metyrapone can also be considered.

Early diagnosis and expert management are crucial given the potential for long-term adverse health outcomes from prolonged hypercortisolism and from morbidity associated with transsphenoidal surgery or radiotherapy. Children with Cushing's syndrome should be referred to multidisciplinary centres of excellence with paediatric endocrinologists expert in managing disorders of the pituitary, and with specialised neurosurgery units. If an underlying genetic syndrome is present, genetic counselling for the child and family members, as well as investigations into other disorders associated with the syndrome, are necessary.[270,274,275]

***Panel 4*: Future research topics ranked of highest importance**

Screening and diagnosis of Cushing's syndrome

- Optimise pituitary MRI and PET imaging using improved data acquisition and processing to improve microadenoma detection
- Compare diagnostic algorithms for the differential diagnosis using invasive versus non-invasive strategies
- Identify additional corticotroph adenoma mutations and develop a comprehensive panel of genomic and proteomic tests for corticotroph adenomas

Complications of Cushing's disease

- Define use of anticoagulant prophylaxis and therapy in different populations and settings
- Optimise the approach in managing long-term complications

Treatment of Cushing's disease

- Determine clinical benefit of restoring the circadian rhythm, potentially with a higher night-time medication dose
- Identify better markers of disease activity and control
- Develop new, better tolerated, more effective medical therapies
- Define populations that might benefit from preoperative medical treatment

Search strategy and selection criteria

References for this review were identified through searches of PubMed for articles published from Jan 1, 2015, to April 30, 2021, using the terms "diagnosis," "urinary free cortisol," "salivary cortisol," "screening tests," "confirmatory testing," "differential diagnosis," "localization testing," "genetics," "surgery," "radiation therapy," "medical therapy," "biochemical treatment goals," "tumor shrinkage," "clinical outcomes," "adrenal steroidogenesis inhibitors," "glucocorticoid receptor blockers," "somatostatin receptor ligands," "dopamine agonists," "mortality," "comorbidities," "quality of life," "preoperative treatment," "combination therapy," and "guidelines" in combination with the terms "Cushing's disease" and "ectopic Cushing's". English-language articles resulting from these searches and relevant references cited in those articles were reviewed.

Conclusions

Academic investigators and clinical experts from 13 countries across five continents gathered virtually to discuss recent evidence regarding Cushing's disease. Consensus was reached on many recommendations for diagnosis and management; these have been presented, along with highlighted areas needing further research in this challenging condition (panel 4).

Contributors

MF, BMKB, AGi, and SM initiated and conceived the consensus meeting. MF and BMKB served as co-chairs and project administrators and supervisors. MF, BKMB, JN-P, NK, MGa, AT, SP, LN, PM, AGi, and SM served as steering committee members; developed the workshop topics; identified expert speakers, participants, and breakout group assignments and moderators; and developed the first draft of the manuscript on the

basis of speaker slide-lecture presentations and précis, and participant breakout discussion comments. MF, BMKB, EVV, GV, and SM contributed to development of the tables, figures, and panels. MF, BMKB, AGi, SM, JN-P, NK, MGa, AT, SP, LN, PM, EVV, GV, RA, IB, AB-S, JB, NRB, CLB, MDB, MB, JDC, FFC, FC, PC, JF, EBG, AGr, MGu, KH, AGI, UBK, LK, DFK, AL, AM, MM, AMP, RP, HR, MR, RS, CS, IS, CAS, BS, AT, YT, MT, ST, EV, JW, SMW, and MCZ reviewed the entire manuscript, approved the final version, and made the decision to submit.

Declaration of interests

MF has received grants to her institution from Novartis, Strongbridge, Novo Nordisk, Crinetics, Millendo, Ascendis, and Pfizer; personal honoraria for consulting and advisory boards from Crinetics, HRA Pharma, Novartis, Recordati, Strongbridge, Sparrow, Ascendis, Novo Nordisk, and Pfizer; and has served on the Board of the Pituitary Society. RA has received grants to his institution from Strongbridge Biopharma, Novartis Pharmaceuticals, and Corcept Therapeutics, and personal honoraria for consulting and advisory boards from Strongbridge Biopharma, Recordati Rare Diseases, Corcept Therapeutics, and Novartis Pharmaceuticals. IB has received grants and fees for consulting, advisory boards, and authorship to her institution from the National Institutes of Health (NIH), Strongbridge, Corcept, HRA Pharma, Sparrow Pharmaceutics, Adrenas Pharmaceutics, and Elsevier, and non-financial support to her institution from HRA Pharma. AB-S has received personal honoraria for advisory boards from Recordati. JB has received grants to his institution from Novartis, HRA Pharma, and Recordati, and personal honoraria for consulting, lectures, and meeting attendance from Novartis, HRA Pharma, Ipsen, and Recordati. NRB has served on the Board or as an advisor for European Neuroendocrine Association and the European Reference Network on Rare Endocrine Conditions. CLB has received grants and personal honoraria for lectures from Novartis and served on the Board or as an advisor for Sociedade Brasileira de Endocrinologia e Metabologia, Endocrine Society, and European Society of Endocrinology. MDB has received grants as principal investigator from Novartis. 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AL has received grants from Recordati and Corcept; personal honoraria for lectures, support for meeting attendance, and advisory boards from Pfizer, Ipsen, Corcept, and the European Journal of Endocrinology; royalties from UpToDate Endocrinology; and served as a Board member for International Society of Endocrinology. AM has received grants and personal honoraria for lectures or presentations and support for meeting attendance from Pfizer, Ipsen, Novartis, and Novo Nordisk, and served as a Council member for Endocrine Society of Australia. SM has received grants to his institution from US Food and Drug Administration and non-financial support from Cyclacel. MM has received grants to his institution from Corcept, Novartis, and Strongbridge; fees for expert testimony from Janssen and Corcept; and personal honoraria for advisory boards for Merck, Pfizer, Recordati, and Strongbridge. 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BMKB has received grants to her institution from Novartis, Opko, Strongbridge, and Millendo; personal honoraria for consulting from Aeterna Zentaris, Ascendis, Crinetics, Merck Serono, Novartis, Novo Nordisk, Recordati, Strongbridge, and Sparrow; and served as an advisor for Endocrine Society. MB, KH, PM, BS, EVV, and JW have no competing interests.

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