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

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Review

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

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Initial treatment of Cushing's disease & monitoring for recurrence

Pituitary surgery

- Transsphenoidal surgery is recommended as firstline therapy for patients with Cushing's disease. 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. Patients in remission require glucocorticoid replacement until HPA axis recovery.

Pituitary surgery

- Treatment at a highvolume 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.

- Newonset 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; perioperative mortality is <1%.

Clinical considerations & 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). Surgery should be done by an experienced pituitary neurosurgeon with followup by a multidisciplinary team including a pituitary endocrinologist (high quality, strong recommendation). Outcomes of pituitary surgery and costeffectiveness (low quality, discretionary recommendation) should be reported and be made publicly available.

Monitoring for recurrence

- Low or undetectable cortisol concentrations in the immediate postoperative period is a defining criterion of remission, but does not necessarily predict lack of recurrence
- 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.
- Lifelong monitoring for recurrence is required

Monitoring for recurrence

- Compared with use in the initial diagnosis of Cushing's syndrome, LNSC, 1mg DST, UFC, and desmopressin tests have a lower sensitivity for recurrence, but specificity is high. LNSC can detect postoperative elevated cortisol concentrations earlier than 1mg DST, and UFC is usually the last test to show abnormal findings in patients who recur. Thus, LNSC could allow for earlier intervention, but serial tests are advised due to wide variability in results.

- Evaluation for recurrence should begin after HPA axis recovery, and then annually or sooner if there is clinical suspicion. In practice, however, clinical manifestations and biomarkers can be discordant.

Clinical considerations & 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).

Clinical considerations & recommendations for monitoring recurrence

- 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).
- 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).

	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]

Repeat pituitary surgery

- Repeat transsphenoidal surgery can be considered in patients with biochemical evidence of recurrent Cushing's disease with visible tumour on MRI.

Clinical considerations & 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 does not show tumour presence, reoperation might be appropriate if an experienced surgeon at a highvolume 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.
- Persistent or recurrent Cushing's disease
- Those who are not candidates or refuse surgery, and to control cortisol concentrations in patients undergoing radiotherapy

	Commonly used doses	Efficacy	Adverse effects	Key considerations
Adrenal steroidogenesis inhibitor				
Ketoconazole[175,180–187]	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[180–183,188–192]	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[175,181,182,193–197]	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[175,181,182,198]	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[175,199–201]	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[*180,205]	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[175,182,204–206]	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[181,187–189]	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**

Targeting adrenal steroidogenesis

- ketoconazole
- Metyrapone
- Mitotane
- Etomidate
- Osilodrostat

Ketoconazole

- 400-1600 mg per day
- Rerospectve studies: approximately 65% of patients had UFC normalization initially, but 15-25% escape
- Blocks multiple adrenal enzymes
- Decrease gonadal steroid synthesis; men might experience hypogonadism and gynecomastia
- 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.
- Hepatotoxicity (10–20% of patients) is mostly asymptomatic with mild or moderate increases in liver enzymes (≤5 × ULN), and typically appears within the first 6 months of treatment; these increases seem not to be dosedependent and reverse within 2–12 weeks after dose decrease or discontinuation.

Ketoconazole

- 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.
- Skin rash is observed in approximately 5%.
- There are several drug–drug interactions.

Metyrapone

- 500 mg to 6 g total per day
- UFC normalization in retrospective studies 70%; in a prospective study, 47% at week 12
- 11βhydroxylase inhibitor
- 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.
- 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. Adverse events secondary to hyperandrogenism can limit prolonged treatment, especially in female patients

Osilodrostat

- 4-14 mg total per day
- Phase 3 randomized withdrawal study showed 86% UFC normalisation
- 11βhydroxylase and aldosterone synthase inhibitor.
- Decreases in bodyweight, blood pressure, total cholesterol, and LDL
- Decreased fasting serum glucose and HbA1c.
- Quality of life and depression scores also improved.
- Nausea, anaemia, and headache
- Effects from increased levels of adrenal steroid precursors, including hypokalaemia and hypertension
- Hirsutism
- Improvements seen in clinical features, cardiovascular disease markers, and quality of life.

Mitotane

- 500 mg to 4 g total per day
- Retrospective studies showed 80% UFC normalisation
- Induction of CYP3A4mediated rapid inactivation of cortisol leads to a requirement for a 2–3times increased glucocorticoid replacement dose when treatment of adrenal insufficiency is needed.
- Most workshop participants considered that use of mitotane should be limited to patients with adrenal carcinoma.

Etomidate

- 0.04-0.1 mg/kg/h intravenously; 0.025 mg/kg/h for patients not in ICU to 4 g total per day
- Retrospective studies showed approximately 100% serum cortisol control (10-20 μg/dl
- 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.
- Associated with thrombophlebitis and pain on injection.
- Haemolysis and renal tubular injury, as well as lactic acidosis at high doses.

Targeting pituitary somatostatin & 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, although only pasireotide is approved by regulatory agencies for use in this population. 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

- **Pasireotide**: 0.6-1.8 mg/ml subcutaneously total per day, given twice a day, Phase 3 study showed 15-26% UFC normalization.
- **Pasireotide long-acting**: 10-30 mg per month, intramuscularly, Phase 3 study showed 40% UFC normalization; clinical signs and symptoms of hypercorticolism improved.
- Between a third and twothirds of Cushing's disease tumours harbour a mutation in *USP8*, and these mutated tumours can show higher SST5 expression compared with wildtype tumours. Because pasireotide has a high affinity for this receptor, *USP8* mutational status might prove to be a useful marker for predicting treatment response.
- The high rates of hyperglycaemia are thought to result from inhibition of insulin and incretin secretion combined with a lesser degree of glucagon inhibition. Management with GLP1 receptor agonists or DDP4 inhibitors is therefore thought to be useful.

Cabergoline

- 0.5-7 mg total per week, orally.
- Retropective studies showed approximately 40% UFC normalization initaially, but roughly 25-40% escape; clinical signs and symptoms of hypercorticolism improved.
- Patients with Nelson’s syndrome can also respond to cabergoline, and both ACTH normalization and tumour shrinkage have been reported. Although not approved in this setting, cabergoline has been used in pregnant patients with prolactinomas and other pituitary adenomas, including Cushing’s disease.
- Cabergolineinduced impulse-control disorder is probably underreported, and can manifest as hypersexuality, pathological gambling, excessive alcohol consumption, overeating, and uncontrolled shopping.
- Although one study in prolactinomas found that moderate tricuspid regurgitation was more frequent with higher doses, a large multicentre study found no association between the cumulative cabergoline dose and agecorrected prevalence of any valvular abnormality

Targeting the peripheral tissue glucocorticoid receptor
Mifepristone

- 300-1200 mg total per week, orally
- Open-lable phase 3 study showed significant improvement in glycaemia (approximately 60% of patients) and blood pressure; clinical signs and symptoms of hypercorticolism improved.
- Endometrial hypertrophy and irregular menstrual bleeding were also reported, consistent with the antiprogesterone activity of mifepristone.
- 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.

Targeting the peripheral tissue glucocorticoid receptor
Mifepristone

- Continued mifepristone treatment of 27 patients with Cushing's disease included in a longterm 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.
- Thyroid function should be closely monitored and thyroid hormone replacement adjusted as needed.
- drug–drug interactions

Clinical considerations & 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
- In patients with severe disease, the primary goal is to treat aggressively to normalise cortisol concentrations (or cortisol action if using mifepristone)

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)

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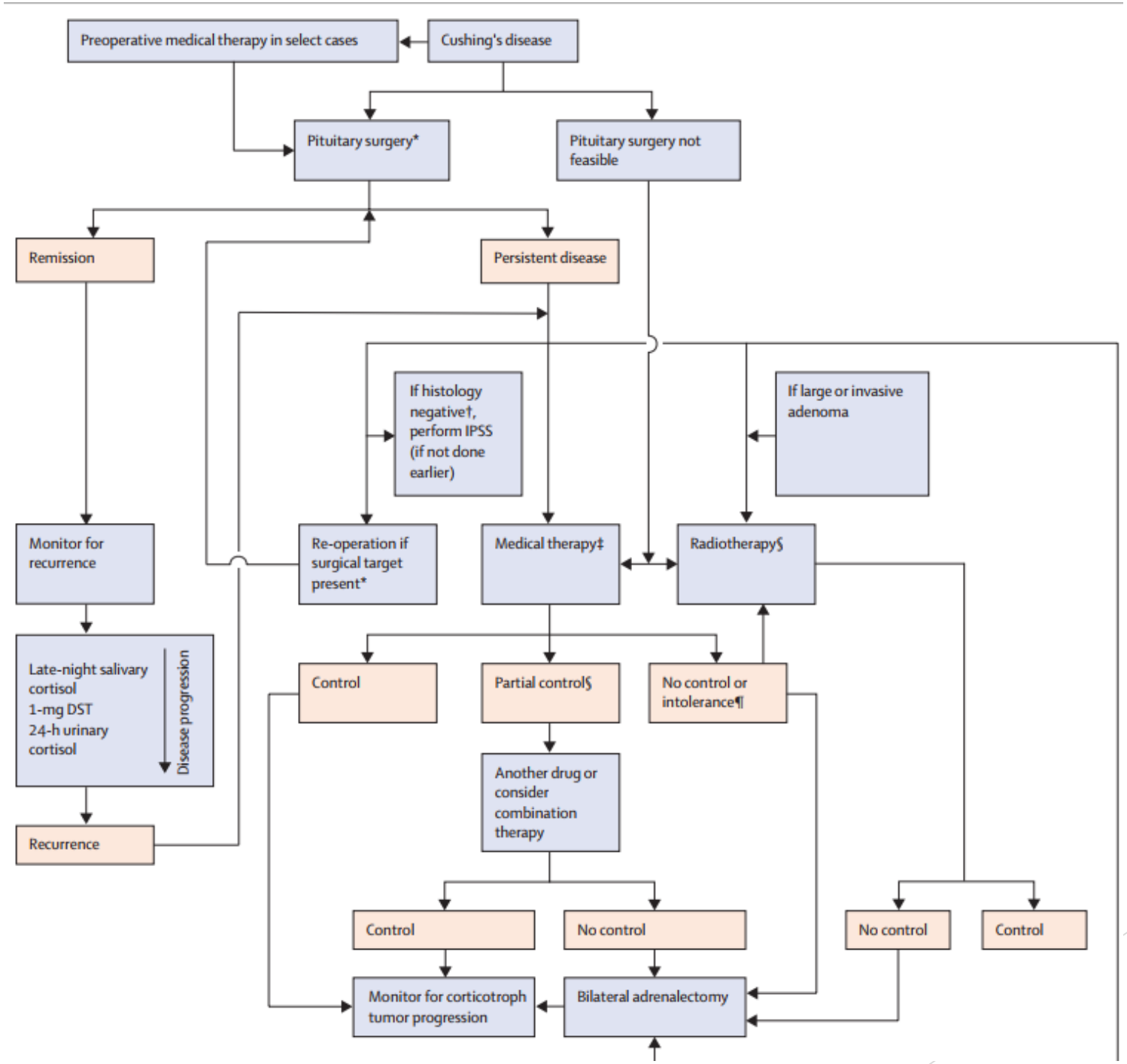
- Change in treatment should be considered if cortisol levels are persistently elevated after 2–3 months on maximum tolerated doses (moderate quality, strong recommendation)
- If cortisol does not normalise but is reduced or there is some clinical improvement, combination therapy can be considered (low 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)


Preoperative medical therapy in select cases
Cushing's disease
Pituitary surgery*
Pituitary surgery not feasible
Remission
Persistent disease
If histology negative†, perform IPSS (if not done earlier)
If large or invasive adenoma
Monitor for recurrence
Re-operation if surgical target present*
Medical therapy‡
Radiotherapy§
Late-night salivary cortisol
1-mg DST
24-h urinary cortisol
Disease progression
Control
Partial control§
No control or intolerance¶
Recurrence
Another drug or consider combination therapy
Control
No control
No control
Control
Monitor for corticotroph tumor progression
Bilateral adrenalectomy

Initial treatment selection for medical therapy

- Adrenal steroidogenesis inhibitors
- ketoconazole, osilodrostat, metyrapone, cabergoline
- For patients with mildtomoderate disease and some residual tumour, there might be a preference for cabergoline or pasireotide
- 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.

Clinical considerations & recommendations for medical therapy

- 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.

Clinical considerations & recommendations for medical therapy

- 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 cutoff target for cortisol (eg, 1·5×ULN) is used.

Clinical considerations & recommendations for medical therapy

- Mifepristone improves key clinical features associated with hypercortisolism, specifically hyperglycaemia and weight gain 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 half-life of mifepristone and its metabolite requires several days of stress-dose glucocorticoid replacement, preferably dexamethasone,

Clinical considerations & recommendations for medical therapy

- Combining ketoconazole with metyrapone
- Steroidogenesis inhibitor plus a tumourtargeting agent, such as ketoconazole plus cabergoline
- Triplets of cabergoline, pasireotide, plus ketoconazole
- Metyrapone, ketoconazole, plus mitotane

Selecting an adrenal steroidogenesis inhibitor

- ketoconazole
- metyrapone
- Osilodrostat
- Mitotane (Rarely used for patients with Cushing's disease in most centres, has a slower onset of action)

Monitoring response to medical therapy

- Measures of cortisol (except with mifepristone)
- Symptoms and comorbidities, especially weight, glycaemia, and blood pressure. quality of life
- Morning cortisol, LNSC, or both could be used as an alternative

Monitoring response to medical therapy

- 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).

Monitoring response to medical therapy

- 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.

Monitoring response to medical therapy

- 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.

Monitoring response to medical therapy

- With adrenaltargeting agents, there can be concern for tumour growth due to ACTHcortisol 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 halflife and concentrations fluctuate, and so they might not necessarily reflect tumour growth. If progressive increase in tumour size is noted, 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.

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.
- A metaanalysis showed no differences in cortisol normalisation rate between participants who received cortisollowering medications in the preoperative setting versus later use as adjuvant treatment.

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

- 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 observe in only a third of cases.

Clinical considerations & recommendations for primary & 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 lifethreatening metabolic, psychiatric, infectious, or cardiovascular or thromboembolic complications might also benefit from preoperative medical therapy in select cases (low quality, discretionary recommendation).

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

- 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).

- 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 or for aggressive tumour growth.

- 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.

Radiotherapy

- Given the latency until postradiotherapy remission, adjuvant medical therapy is needed to control hypercortisolism

- Although data are mixed on whether ketoconazole or cabergoline treatment at the time of stereotactic radiosurgery limits efficacy, they are often withheld temporarily at the time of radiotherapy

Radiotherapy

- Hypopituitarism is the most common side-effect of both conventional radiotherapy and stereotactic radiosurgery, seen in 25–50% of patients
- Risk of secondary malignancy, cranial nerve damage, and stroke are low 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.

Clinical considerations & 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

- 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. 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.

Clinical considerations & 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).
- 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).

Clinical considerations & recommendations for adrenalectomy

- 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).

Genetics of Cushing's disease

- Corticotroph adenomas are predominantly of sporadic origin, based on a monoclonal expansion of a singular mutated cell. These adenomas abundantly express EGFR, which signals to induce ACTH production.
- Somatic activating driver mutations in *USP8* are present in 36–60% of corticotroph adenomas. These mutations lead to persistent overexpression of EGFR, thereby perpetuating the hyper-synthesis of ACTH.
- *NR3C1*
- *BRAF*
- Deubiquitinase *USP48*
- *TP53*
- familial tumour syndromes, such as *MEN1, FIPA,* and *DICER1*, rarely develop corticotroph adenomas

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.
- screening is usually reserved for cases in which there is either family history or other signs suggestive of a genetic syndrome.
- Lack of height increase concomitant with weight gain.

Diagnosis and management of Cushing's syndrome in children

- Documentation of hypercortisolism with 24h 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. The DexCRH test is not useful in children. In children older than 6 years, Cushing's disease is the most common cause of Cushing's syndrome.

- The role of IPSS in children is more limited than in adults.

Diagnosis and management of Cushing's syndrome in children

- As in adults, surgical resection of the ACTHsecreting tumour is the firstline 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. Evaluation for growth hormone deficiency should be done by 3–6 months postoperatively, and immediate growth hormone replacement given if needed.
- 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. Blockandreplace regimens with metyrapone.

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.

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

Thanks for your Attention