

Cushing's disease: current trends in treatment

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Practice Points

- Diagnostic work-up of Cushing's disease should be performed in an experienced endocrine center as it guides subsequent management.
- Trans-sphenoidal surgery remains the gold-standard treatment.
- Radiotherapy is a second-line option.
- Bilateral adrenalectomy is still used and valued in difficult cases.
- Medical agents have their place, when any other treatment/its effects are awaited or unsuccessful.

SUMMARY: Cushing's disease (CD) is an uncommon endocrine disorder resulting from an adrenocorticotrophin-producing pituitary adenoma. Its clinical features and subsequent comorbidities are the consequence of hypercortisolism and may be life-threatening if untreated. Trans-sphenoidal selective adenomectomy or hypophysectomy remain recommended first-line treatments for CD and may be repeated if unsuccessful or following recurrence of the tumor. Pituitary radiotherapy, either conventional fractionated external beam or in the form of radiosurgery, is a second-line treatment option, but its effects are delayed for several years. Bilateral adrenalectomy is a valuable treatment option for acutely unwell patients or for those who are unable to take or tolerate medical therapy. Steroidogenesis inhibitors such as metyrapone, ketoconazole, etomidate and mitotane have their place at many stages in the management of CD and are usually very effective. Pituitary tumor-targeted agents, such as cabergoline or pasireotide, remain as second-line medical treatment options, but are effective in only some 25–30% of patients.

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Cushing's syndrome (CS) is a rare endocrine condition in which clinical features result from an excess of corticosteroids. Endogenous CS has an incidence of two to three cases per million of the population per year, and in 80–85% of patients it is caused by excessive production of adrenocorticotrophin hormone (ACTH) by a pituitary adenoma (Cushing's disease [CD]) or an ectopic tumor [1]. CD is responsible for 80–90% of ACTH-dependent CS and in adults it is most common in women, while there is a male predominance in prepubertal children [2]. In 90% of cases it is caused by a pituitary microadenoma with an average diameter of 6 mm. ACTH-dependent ectopic CS can be caused by small-cell lung cancer, bronchial carcinoid, pheochromocytoma, medullary carcinoma of the thyroid, or neuroendocrine tumors of the pancreas, GI tract or thymus.

ACTH-independent CS is a consequence of overproduction of cortisol by an adrenal adenoma or carcinoma or, less frequently, bilateral adrenal hyperplasia in the form of primary pigmented nodular adrenal dysplasia (associated with Carney complex) or ACTH-independent macronodular adrenocortical hyperplasia.

Investigations of CS start with clinical suspicion of the syndrome with the most distinctive signs, including proximal myopathy, purple striae, central obesity with facial plethora, bruising and unexpected osteoporosis. Less specific features are hirsutism, acne, dysmenorrhea, low mood or psychosis, hypertension, impaired glucose tolerance or diabetes. In children, the most suggestive signs of CS remain obesity associated with retardation of growth.

It is estimated that approximately 1% of the population uses different forms of corticosteroids as a treatment for numerous medical conditions, thereby causing exogenous CS. Therefore, before a diagnosis of endogenous CS is made, the patient's medications need to be scrupulously reviewed, including prescribed topical, nasal, inhaled, intraocular, intra-articular and 'over-the-counter' preparations.

The recommended screening tests include the overnight dexamethasone suppression test (1 mg at midnight; serum cortisol at 9 am the following morning should be <50 nmol/l), late-night salivary cortisol (if available, at least two tests) or 24-h collection for urinary-free cortisol. The urinary-free cortisol is the least sensitive and reliable, but if used it is recommended that a

minimum of three collections are required [3]. When two of the above tests are positive, a referral to a specialist endocrinologist should be made for further investigations.

In our endocrine department the patient is admitted to hospital for subsequent investigations, which start with confirmation of CS with an elevated midnight sleeping serum cortisol on two occasions and a lack of suppression of 9 am cortisol on the low-dose dexamethasone suppression test (0.5 mg 6-hourly for 48 h; 9 am serum cortisol should be <50 nmol/l) with baseline ACTH measurement. A plasma ACTH above 20 ng/l (reference range 10–50 ng/l) points towards ACTH-dependent CS, and MRI scanning of the pituitary is then arranged.

Once ACTH-dependent CS is confirmed, differentiation of CD from ectopic ACTH secretion is assisted by noting a fall in cortisol during the low-dose dexamethasone test (a fall from baseline >30% suggests CD) [4] and the corticotrophin-releasing hormone (CRH) stimulation test, where an increase above baseline of ACTH by 30–50% and cortisol by 15–20% suggests a pituitary source of ACTH [5]. The CRH test also helps establish ACTH dependence where the basal ACTH level is in the range of 10–20 ng/l. If available, bilateral inferior petrosal sinus sampling remains the gold-standard investigation in differentiating pituitary from ectopic ACTH-dependent CS, which, in our center, is performed in almost all cases of ACTH-dependent CS, except for patients with a pituitary macroadenoma (>1 cm in diameter). In some endocrine centers it is reserved only for patients in whom a pituitary adenoma cannot be identified on imaging. A CRH-stimulated ACTH gradient between inferior petrosal sinus and peripheral blood of more than 3:1 confirms a pituitary source of ACTH and interpetrosal ratio, and helps with lateralization of the pituitary adenoma, when the MRI scan fails to identify a lesion [6]. Venography preceding inferior petrosal sinus sampling helps identify asymmetrical drainage from the pituitary gland or the presence of shunting, which should be taken into account when interpreting the results. An exploration of the remaining gland is recommended if an adenoma is not found on the predicted side [7].

We have recently summarized the investigations used in the differential diagnosis of CD and provided our current algorithm [8].

Treatment

The aim of treatment in CD is to: restore normocortisolemia; reverse or improve consequences of CS such as diabetes, hypertension and hypokalemia, muscle atrophy, enhanced cardiovascular risk, depression, impairment of memory and quality of life; and in cases of pituitary macroadenomas, to establish long-term control of the tumor growth and reversal of optic chiasm compression, if present. Those may be achieved by trans-sphenoidal surgery, radiotherapy (RT), bilateral adrenalectomy (BA) and medical treatment.

■ Trans-sphenoidal surgery

Selective endoscopic trans-sphenoidal adenectomy via the transnasal approach is the recommended treatment of choice for CD. If the tumor is not identified easily during surgery, hemihypophysectomy could be performed; this will be guided by the preoperative MRI scan finding and the results of bilateral inferior petrosal sinus sampling.

Biochemical 'cure' is defined by a 9 am cortisol of <50 nmol/l (1.8 µg/dl) after withholding hydrocortisone replacement for more than 12 h in the first week after trans-sphenoidal adenectomy. If it remains elevated above this cut-off value on repeated testing, we perform a five-point cortisol day curve. Levels between 50 and 300 nmol/l (1.8–10.8 µg/dl) are consistent with remission, while levels above 300 nmol/l define treatment failure [9].

The success rate is highly dependent on a skilled neurosurgeon, who performs a sufficient number of procedures per year. The literature review of the results from many endocrine centers reveals total cure and remission rates of 65–90% for pituitary microadenomas causing CD and 45–60% for macroadenomas, using the above criteria [9]. A study of 131 patients from St Bartholomew's Hospital in London (UK) demonstrated a total cure and remission rate of 67.7% at a mean time of 15 years following surgery, but these results have been improving over time and currently a combined cure and remission in the order of 90% should be achievable in experienced centers [10].

Even after selective adenectomy, corticotrophic cells of the remaining pituitary gland are not able to have their function restored immediately due to previous chronic suppression by supra-physiological levels of cortisol. Therefore, patients

require hydrocortisone replacement. The lack of recovery of the hypothalamo–pituitary–adrenal axis in the first 3 years following surgery was found to be the best predictor of long-term cure in the cohort from St Bartholomew's Hospital in London [10]. According to other studies, good predictors of cure of CD include histologically confirmed corticotroph adenoma, microadenomas, a preoperative lack of cavernous sinus involvement and low postoperative cortisol levels [11–13].

The recurrence rate of CD secondary to microadenoma, following initial surgery, increases with time and is approximately 5–10% at 5 years and 10–20% at 10 years of follow-up [11–15]. As expected, it is higher for macroadenomas and ranges from 12 to 45%, and occurs earlier at a mean time of 16–37 months of surveillance [16–18]. Therefore, life-long follow-up is advised for all patients.

Trans-sphenoidal surgery can be repeated in case of failure of biochemical cure and residual disease, as well as for recurrence of the tumor. The success rate of a subsequent operation is lower and results in biochemical remission in 50–60% of patients with slightly higher remission rates if a microadenoma is visualized during surgery [19,20]. Total hypophysectomy may be an option, especially in older patients, but needs to be followed with life-long replacement of pituitary hormones.

■ Radiotherapy

RT is a useful second-line treatment for CD, which controls tumor growth and normalizes hormonal secretion. It is very effective, but may require many years to see the full therapeutic effect in adults, although an earlier onset of action is observed in children [21].

Most experience with this treatment modality comes from conventional external-beam RT, which is generated from a linear accelerator in the form of three to five beams and delivered in 25–30 fractions to a total dose of 45–50 Gy; nowadays, this is usually stereotactic fractionated conformal RT. Another option involves stereotactic radiosurgery ('γ-knife') as a single dose delivered through multiple portals [22]. The dose used in γ-knife surgery is 18–24 Gy. The optic chiasm can tolerate a single dose of 8–10 Gy, therefore, to avoid damage to the optic nerves during radiosurgery, it should be delivered to the tissue that is at least 5 mm distant [23].

Currently available precise imaging techniques using MRI and CT scanning help with RT planning/delineation of the pituitary tumor and reduce radiation of normal brain tissue to the minimum. To facilitate the precision of treatment, which is especially important if delivered in multiple fractions, every patient has an individualized plastic mask constructed during their first appointment. This allows only 2–5 mm movement in conventional RT and only 1–2 mm movement in radiosurgery, where immobilization is achieved by using a metal frame screwed to the skull.

Several studies analyzing the outcomes of conventional RT report tumor control in 93–100% of patients at a median follow-up of 8 years (3.5–12.4 years) and normalization of cortisol levels in 46–84% of patients in the same follow-up time [22,24–26]. Data related to the results of radiosurgery are claimed to show significantly shorter median follow-up time of 45 months with comparable tumor control in 94% of patients and hormonal normalization achieved in 48% in 6–36 months' time [27–29], but no head-to-head comparison of conventional versus radiosurgical RT has been performed. A study by Castinetti *et al.* of 76 patients with secretory adenomas and a longer follow-up time of 96 months showed biochemical remission in 44.7% of patients [30]. Other radiation techniques, such as proton-beam therapy, are of limited availability and there is little evidence that they offer any advantages.

The most common complication of RT is hypopituitarism, with one or more hormonal deficiencies in 20–40% of patients at 10 years' follow-up, regardless of the mode of delivery of RT. Optic neuropathy with a visual field deficit is reported in 0–4% [31], secondary brain tumors such as meningioma in 2% of patients at 20 years [32], and necrotic brain injury in 0–2% of patients [33]. RT is associated with a relative risk of cerebrovascular accidents of 4.1 compared with an age-matched population [34]. Following radiosurgery, in one series 10% of patients (nine out of 90 patients) developed cranial nerve deficits with ophthalmoplegia due to third or sixth nerve palsy in 4.5% [28].

RT is also used for prevention and treatment of Nelson's syndrome, defined as the autonomous growth of a pituitary adenoma following BA for uncontrolled CD; it is reported in 30–50% of patients [35]. In several studies, conventional

prophylactic RT achieved pituitary tumor control in 75–100% of patients with Nelson's syndrome at a median time of 8 years [24].

■ Bilateral adrenalectomy

BA provides definitive and immediate control of hypercortisolism. Therefore, it is recommended in patients with severe CD, when transphenoidal surgery failed to control the disease and medical treatment is poorly tolerated or ineffective; following RT to the pituitary tumor, BA may still be required to establish control of the excess cortisol. This treatment option is particularly valued in women planning pregnancy, where RT may cause gonadotrophin deficiency and thus necessitate ovulation stimulation treatment in the future.

BA should be performed via a minimally invasive endoscopic approach or traditional open adrenalectomy via the anterior or posterior approach. BA performed by the da Vinci (Intuitive Surgical, CA, USA) robot has also been reported [36]. When the laparoscopic/robotic technique is applied, postoperative recovery is quicker with a median hospital stay reduced to 3 days and comorbidities minimized [37].

If this modality of treatment is chosen, future compliance with life-long gluco- and mineralocorticoid replacement has to be taken into consideration. This will require education of the patient regarding an adjustment of the dose of steroids when unwell.

Nelson's syndrome remains the most serious complication of BA [38]. As BA normalizes cortisol levels with no direct effect on the ACTH-secreting pituitary adenoma, it can continue to grow, causing a local pressure effect, and become clinically apparent by gradually increasing skin pigmentation from excess of melanin stimulated by high levels of ACTH. Therefore, in some endocrine centers, prophylactic RT of the pituitary tumor is performed. In our center, if pituitary residual disease is small and/or not visualized on imaging, we opt for annual MRI surveillance and a yearly assessment of ACTH levels [35].

■ Medical therapy

Medical therapy for CD may be used at different points in the management algorithm for CD: immediately after diagnosis when the patient is being prepared for surgery; if and when surgery fails; in preparation for BA, when RT or its

effect is awaited; or finally, when other treatment options have been tried but failed to control the hypercortisolemia.

Medical agents utilized in CD are divided into adrenal- and pituitary tumor-directed (Table 1). The first group includes steroidogenesis inhibitors, such as metyrapone, ketoconazole, mitotane and etomidate, and these are most often used and most effective. The second group contains medications acting centrally, such as cabergoline or pasireotide, although

to date these are less impressive in controlling CD. Mifepristone is a glucocorticoid receptor antagonist that can be used as adjuvant therapy.

Adrenal-targeted therapy

■ Metyrapone

Metyrapone is a first-line steroidogenesis inhibitor used in the UK and in some other European countries, but which is currently available only for compassionate use in the USA. It decreases

Table 1. Medical therapy for Cushing's disease.

Medication	Action	Dosage	Form	Side effects	Comments
Adrenal-directed therapy					
Metyrapone	11 β -hydroxylase inhibitor	250–1000 mg t.i.d.–q.i.d. maximum 6 g/day	Oral	Gastrointestinal upset, acne, hirsutism, hypotension or hypertension, edema, hypokalemia, sedation	First-line treatment when available, avoid long-term use in young women
Ketoconazole	11 β -hydroxylase; 17,20-lyase inhibitor	200–400 mg t.i.d.	Oral	Gynecomastia, alopecia, reduced libido, hepatotoxicity, gastrointestinal upset, rashes	Slow in onset of action, first-line in children, stop PPI/H2 antagonist as gastric acid needed for absorption
Mitotane	Adrenolytic	500–1000 mg t.i.d.–q.i.d., gradually increased from 500–1000 mg/day to maximum 6 g/day	Oral	Gastrointestinal upset, deranged LFTs and TFTs, hypercholesterolemia, ataxia, teratogenic, orthostatic hypotension	Slow in action, third-line treatment, increases CBG, accumulates, now rarely used for CD
Etomidate	11 β -hydroxylase, 18-hydroxylase 17,20-lyase inhibitor	0.01–0.5 mg/kg/h Starting rate 2 mg/h	Intravenous infusion	Sedation, nausea and vomiting, temporary uncontrolled muscle movements, rash, angioedema	Parenteral, rapid onset of action, anesthetic agent, frequent monitoring of cortisol required
Pituitary tumor-directed therapy					
Cabergoline	Dopamine agonist	1–7 mg/week	Oral	Postural hypotension, nausea, sedation, hallucinations, edema, depression, possibility of heart valve sclerosis	May be tried as third-line treatment, direct corticotroph effect
Pasireotide	Somatostatin analog	600–900 μ g twice daily	Subcutaneous injection	Hyperglycemia, cholelithiasis, diarrhea and vomiting, headache	Effective only in mild CD, treatment of hyperglycemia frequently required
Other agents					
Mifepristone	Glucocorticoid receptor antagonist	300–1200 mg/day	Oral	Nausea, vomiting, dizziness, headache, arthralgia, increased TSH, decreased HDL, endometrial thickening, rash, edema	Cortisol and ACTH levels remain high so hypokalemia may persist, monitoring difficult, also antiprogesterone

ACTH: Adrenocorticotrophin hormone; CBG: Cortisol-binding globulin; CD: Cushing's disease; HDL: High-density lipoprotein; LFT: Liver function test; PPI: Proton pump inhibitor; q.i.d.: Four-times daily; TFT: Thyroid function test; t.i.d.: Three-times daily; TSH: Thyroid-stimulating hormone. Adapted with permission from [1].

cortisol and aldosterone levels by blocking 11 β -hydroxylase, which increases their precursors and redirects steroidogenesis to adrenal androgen production; therefore, it may not be the best choice of agent in young women. The usual starting dose is 250 mg three-times daily, which may be increased if needed to a maximal dose of 6 g/day in divided doses, aiming for a mean cortisol of 150–300 nmol/l (5.4–10.8 μ g/dl) [39] on a five-point cortisol day curve. However, as 11-dexycortisol may cross-react in conventional cortisol assays, possibly a slightly lower level may need to be targeted if using newer mass spectrometry-based assays [9]. Metyrapone has a relatively rapid onset of action and the desired cortisol levels are achieved in 75% of patients after 2 weeks of treatment [40].

This medication is relatively well tolerated but higher doses may cause symptoms of hypoadrenalism with anorexia, nausea, vomiting and weight loss. Excess of mineralocorticoid precursors may cause persistent hypertension, edema and hypokalemia, despite normalized levels of cortisol. Increased adrenal androgens in women may contribute to persistent/new-onset hirsutism and acne [9,41].

■ Ketoconazole

Ketoconazole is an imidazole derivative known for its antifungal properties. It can be used as a first-line agent or added to metyrapone. It decreases cortisol and aldosterone levels by inhibiting 11 β -hydroxylase and lowers adrenal androgen levels by blocking 17,20-lyase [42,43]. Due to the latter effect it is the preferred agent in women. The initial dose is 200 mg twice a day, which can be titrated to 400 mg three-times daily. It is slower in onset of action in comparison with metyrapone, needing several weeks to decrease cortisol levels; because it requires gastric acidity for absorption, medications lowering gastric pH should be discontinued.

Valassi *et al.* reviewed 62 patients treated with ketoconazole, metyrapone or both preoperatively for a median time of 4 months and reported biochemical control of hypercortisolism in 52% of patients [44].

The most frequent adverse effect of ketoconazole is deranged liver function, which occurs in up to 15% of patients and usually during the first week of treatment, although levels not exceeding three-times the upper normal limit do not require cessation of therapy [9]. A fulminant liver

failure has been reported in several cases and its incidence is estimated at one per 15,000 patients [41,45,46]. Due to its antiandrogen action, men may experience gynecomastia, alopecia and decreased libido, which should prompt checking of their testosterone levels and considering replacement if low. Rarely, patients may complain of gastrointestinal upset and rash.

■ Mitotane

Mitotane is an adrenolytic agent rarely used in CD, and most experience with it comes from treatment of a cortisol-secreting adrenocortical carcinoma. The recommended starting dose is 500 mg at night and it needs to be titrated up every few weeks to the total dose of 3–4 g/day. It is very slow in onset of action, with weeks to months being required to observe its full effect. As mitotane accumulates in fat tissue, it has a very long half-life reaching 150 days; therefore, the effects of treatment are apparent for weeks after discontinuation of the medication [47].

Mitotane increases cortisol-binding globulin level, so total serum cortisol cannot be used for monitoring of treatment and often a 'block-and-replace regimen' with the addition of relatively high doses of hydrocortisone is recommended. In men, testosterone replacement may also be required.

Mitotane is not well tolerated at higher doses, causing lethargy, nausea and vomiting, ataxia, vertigo, abnormal liver and thyroid function, deranged clotting and hypercholesterolemia [39] and significantly impacting on the patients' quality of life. Monitoring blood levels to avoid a level >20 mg/l is recommended. It is teratogenic; therefore, pregnancy should be avoided for 5 years after stopping the treatment [48].

■ Etomidate

Etomidate is known as an anesthetic agent and the only steroidogenesis inhibitor available in the form of intravenous infusion, which makes it valuable in patients who are unable to tolerate oral treatment or with a decreased level of consciousness. It works by inhibition of 11 β -hydroxylase, 18-hydroxylase and 17,20-lyase enzymes [49].

Due to its sedative properties it should generally be administered in an intensive care setting. The recommended starting infusion rate is 2 mg/h, which could be titrated up or down by 0.5 mg/h increments to achieve a target cortisol level of 150–300 nmol/l, but in an acutely unwell

patient, for example in sepsis, blood levels ought to be maintained higher, matching the physiological requirement of 500–800 nmol/l [50].

Etomidate decreases cortisol level very efficiently and the target levels may be attained within a few hours, and thus cortisol and potassium levels need to be monitored 4-hourly as the risk of hypoadrenalism is high. If achieving desirable cortisol levels is difficult without overtreatment, we suggest a 'block-and-replace regimen' with simultaneous infusion of hydrocortisone of 0.5–2 mg/h [50].

The main side effects of this agent are sedation, nausea and vomiting, or uncontrolled muscle movements. However, at the infusion rates shown above we have rarely seen these as problems.

Pituitary tumor-targeted therapy

■ Cabergoline & bromocriptine

Cabergoline and bromocriptine are dopamine receptor agonists widely used in treatment of prolactinoma and in higher doses in acromegaly as an adjuvant therapy to somatostatin analogs. Histopathological studies of corticotroph adenomas showed an expression of D2 receptors on 75–83% of cells [51]; this finding prompted their use in the treatment of CD, although with a rather poor outcome. There have been a few small studies in which a variable response of 1–50% of patients to bromocriptine in doses up to 40 mg/day have been reported [52,53]. Cabergoline 1–7 mg/week was reported to control hypercortisolemia in 25–50% of patients with a 'tumor effect' noted in 20% [51,54], but those were based on 20–30 patients and later treatment escape was noted in some of them. Therefore, cabergoline is not recommended as first- or second-line therapy for CD, but could be attempted when other options have been exhausted.

Dopamine analogs are reasonably well tolerated and the reported side effects comprise nausea, postural hypotension, headaches and hallucinations. It is known that dopamine agonists increase the risk of heart valve regurgitation in patients taking much higher doses for Parkinson's disease. A multinational study of more than 6700 patients taking dopamine agonists (in similar doses to those in CD) for hyperprolactinemia showed no association [55]. Clinicians need to be aware of the rare adverse effect, although with potentially catastrophic consequences for an individual, which is increased

tendency to pathological gambling reported in several cases [56].

■ Pasireotide

Pasireotide is a new somatostatin analog, which, compared with octreotide and lanreotide, has 40-times higher affinity to the somatostatin receptor sub-type 5 (sst5). The sst5 receptor was found expressed predominantly on human corticotroph adenoma cells, and *in vitro* suppressed ACTH release in 30–40% of cells [57]. In 2012, a Phase III multicenter trial with pasireotide included 162 patients with CD; disappointingly, pasireotide was effective only in mild-to-moderate hypercortisolemia, normalizing urinary-free cortisol in 26.4% of patients receiving 900 µg of pasireotide twice a day via subcutaneous injection [58]. The lower dose of 600 µg twice

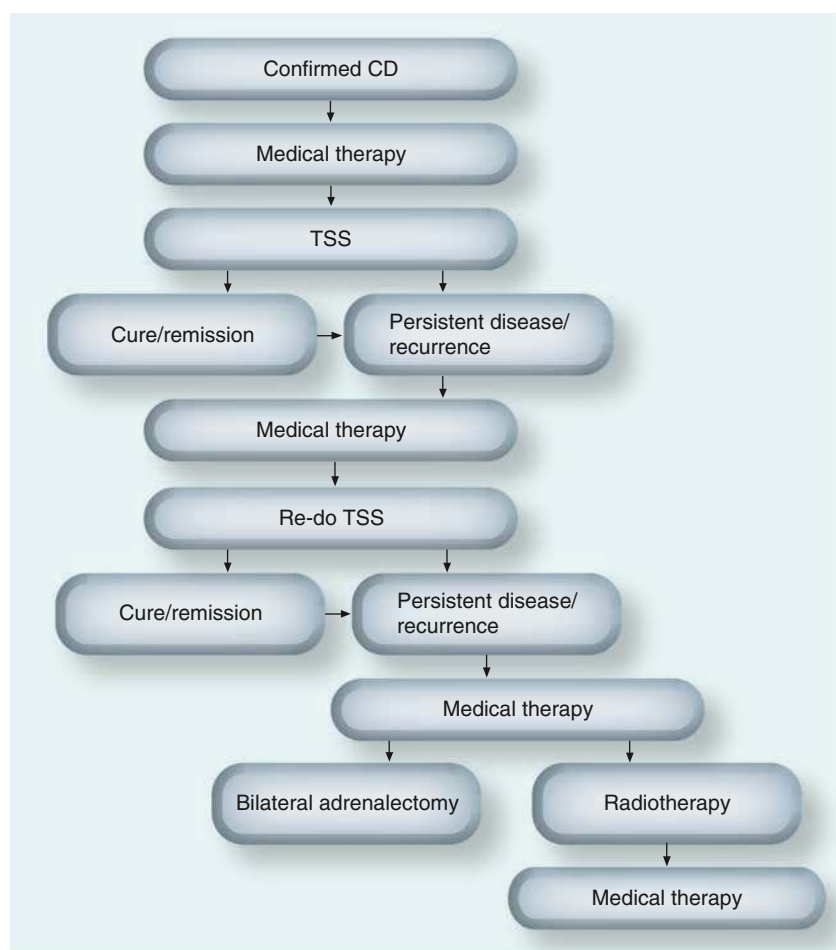


Figure 1. Algorithm of the management of Cushing's disease.

CD: Cushing's disease; TSS: Trans-sphenoidal surgery.

Adapted with permission from [1].

daily was effective in 16% of patients. However, in a subsequent extension study, the agent, when successful, continued to be effective with no tachyphylaxis.

Side effects occurred in the majority of patients, with hyperglycemia reported in 73%, of which 46% required new medication to treat it. Nausea and diarrhea was found in 54%, deranged liver enzymes in 29% and cholelithiasis in 30% of participants [58]. The diabetogenic effect was thought to be principally due to sst5 suppression of insulin and particularly of insulin secretagogues such as the incretins.

Mifepristone

Mifepristone is a glucocorticoid and progesterone receptor antagonist that does not control cortisol levels but blocks its action at the receptor site. In fact, it increases ACTH and cortisol levels, which remain high even when patients have symptoms of hypoadrenalism. This phenomenon is of some clinical concern, as there is no biochemical test to monitor treatment and patients need to be assessed clinically. The recommended dose is 300–1200 mg once-daily by mouth [41].

As the hypercortisolemia persists, it saturates 11 β -hydroxysteroid dehydrogenase type 2, disables conversion of excess of cortisol to cortisone, and thus activates the mineralocorticoid receptor. Therefore, patients can experience worsening hypertension, hypokalemia, fluid retention and congestive heart failure [59]. Other side effects include nausea and vomiting, arthralgia, increased thyroid-stimulating hormone levels and endometrial thickening in women (by blocking the progesterone receptor). Interestingly, mifepristone improved glucose tolerance and mean HbA1c from 7.8 to 6.2% [60], and it has thus been approved in the USA as an adjuvant treatment for CD with associated hyperglycemia. In this

study by Fleseriu *et al.*, diastolic blood pressure improved in 38% of patients with pretreatment hypertension.

Conclusion & future perspective

The treatment of CD remains challenging even to the specialist endocrinologist; this entity is best managed by a multidisciplinary team with the involvement of experienced neurosurgeons, neuroradiologists, endocrinologists and oncologists. Trans-sphenoidal selective adenomectomy is the best first-line treatment, which can be repeated if appropriate. RT is an effective, although delayed, second-line treatment option, and BA could be the only therapeutic option in some circumstances. Medical therapy, especially steroidogenesis inhibitors, proved to be useful at different stages of the management of CD (Figure 1). The success of the treatment is best measured by the resolution of the patient's symptoms and improvement in their quality of life. In the future, it is to be hoped that trials of the combination of cabergoline and pasireotide will provide additional therapeutic opportunities, while pilot studies of a novel 11 β -hydroxylase inhibitor, LC1699 (Novartis, Basel, Switzerland) have shown an easier drug regimen compared with metyrapone, and possibly less virilization. However, we are still some way from an ideal medical therapy.

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