Cyclic Cushing’s Disease

Cushing's syndrome (CS)

- is a general term for diseases caused by chronic excessive exposure to glucocorticoids due to various etiologies and alterations in cortisol circadian rhythm. CS is a relatively **rare** disease, with an annual **incidence** of **0.2–5.0** per million people.
- **Most patients** with CS present with **exogenous hypercortisolism**, while endogenous hypercortisolism is much rarer .
- In 1956, Brike et al. discovered that patients with CS exhibit a periodic increase in cortisol levels, and Bailey formally defined this condition as periodic CS in 1971

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Common alternative terms

- intermittent
- variable
- periodic
- episodic hypercortisolism

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Definition and Prevalence

- A variety of terms have been applied to denote patients with CD who have experienced substantial **fluctuations in biochemical indices** of disease activity ***with or without*** concurrent changes in **clinical features**, including “intermittent hypercortisolism,” “fluctuating steroid excretion,” “unpredictable hypersecretion of cortisol,” “periodic hormonogenesis,” and “cyclic or cyclical CD (or CS).

Cushing book

Definition for cyclic CD

- no universally agreed
- It has **previously** been suggested that **three peaks** and two troughs of hypercortisolism are required at a minimum to define a patient as having cyclic CD.

- In **one recent** study, however, it was suggested that the presence of only one cycle, defined as **two peaks** with an interim trough (or remission) of hypercortisolism, should suffice as a case definition.

- Cushing book
- Diagnostic challenges in cyclic Cushing's syndrome: a systematic review
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Cyclic Cushing's syndrome

- The **cyclic nature** of the condition interferes with the outcome of diagnostic procedures, resulting in both **missed diagnoses** and **misdiagnoses**.
- Patients with cyclic Cushing's syndrome might be **turned away** from physicians when presenting during a **trough phase** (and hence with physiological cortisol concentrations).

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CCS

- CCS **onset varies** from a few days to several months (**usually 12 h to 86 days**), although some studies reported cases with onset periods of > 1 year. CCS is more common in women, with a **male-to-female ratio of 1:3** .
- Compared with CS, CCS patients are **older** (50–60 years) and have a history **of alcohol consumption** (1–7 drinks per week) .
- CCS **rarely** occurs in **children**; however, in children with below-normal linear growth and excessive weight gain, CS cannot be ruled out based solely on one or two cortisol tests showing normal levels, and the possibility of CCS should be considered.
-

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Pituitary tumours **67%**
Ectopic tumours **17%**
Adrenal causes **11%**

in 11%.

Sex

CCS is more common in women, with a male to female ratio of 1:3.

Age

Age 50–60 years

Disease cycle

The onset period of CCS ranged from 12 hours to 510 days, with an average period of 21 days.

Cyclic Cushing's Syndrome

Diagnosis

LNSC, DST and UFC are the most commonly used diagnostic methods.

Studies have found that psychiatric symptoms are more common in patients with CCS versus CS

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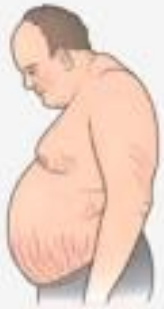

Cortisol secretion patterns

Patients with CCS exhibit at least three peaks and two troughs of cortisol production.

Treatment

Block and replace therapy may be effective in treating CCS.

	Time period	Number of patients with Cushing's syndrome	Definition of cyclicity	Number of patients with cyclic Cushing's syndrome	Main biomarker
McCane et al (1993)[68]	1977–1990 retrospective	41	..	7 (17%, 7–32)	UFC
Streeten et al (1997)[13]	..	33	..	7 (21%, 9–39)	UFC or DST
Powel et al (2008)[69]	1969–2006 retrospective	34	..	9 (26%, 13–44)	UFC
Alexandraki et al (2009)[1]	1946–2007 retrospective	201	Two peaks of cortisol and one trough, clinical and biochemical or biochemical alone	30 (15%, 10–21)	5-point serum cortisol day curves
Jahandideh et al (2018)[42]	2007–2018 retrospective	205	Three peaks of cortisol and two troughs, only biochemical	17 (8%, 5–13)	LNSC or UFC
Jahandideh et al (2018)[42]	2007–2018 retrospective	205	Two peaks of cortisol and one trough, only biochemical	38 (19%,14–25)	LNSC or UFC
Total	1946–2018	514	..	70 (14%, 11–17) to 91 (18%, 15–21)	..

Data are N or n (%, 95% CI). DST=dexamethasone suppression test. LNSC=late-night salivary cortisol. UFC=urinary free cortisol.

Table 1: **Proportion of patients with cyclic Cushing's syndrome in cohorts of patients with Cushing's syndrome**

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Cyclic Cushing’s disease (CD)

- Retrospectively collected data suggest that cyclic CD accounts for approximately **15–19%** of all CD cases. The **pathogenesis** of this condition remains **obscure**.

- Cushing book

Prevalence of cyclic Cushing's syndrome

- Cyclic Cushing's syndrome could account for **7–21%** of patients with **Cushing's disease** and up to ***26%*** of patients with ***micronodular adrenal hyperplasia***.
- Depending on the criteria used, there was an overall proportion of cyclicity of 14% (three peaks and two troughs) to ***18%*** (***two peaks*** and one trough.

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Patient sex of cyclic Cushing's syndrome

- Most patients with cyclic Cushing's syndrome were **female** (169 of 212 [**80%**, 95% CI 74–85] vs 393 of 502 patients with ***non-cyclic*** Cushing's syndrome [***78%,*** 95% CI 74–82; **p=0·6904**).

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Patient age of cyclic Cushing's syndrome

- In the adult population, patients with **cyclic Cushing's syndrome** had a **mean age of 44·9 years** (SD 15·5, range 18–78) compared with 44·1 years (SD 14·7, 19–78) for patients with non-cyclic Cushing's syndrome (**p=0·5871**).
- 23 of the 203 patients with relevant age data (**11%**, 95% CI 7–17) were **children** with a mean age of **10·4 years** (SD 4·4, range 0–17), with more girls being affected by cyclic Cushing's syndrome than boys

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Patient origin of cyclic Cushing's syndrome

- Most **adrenal** causes were due to **micronodular adrenal hyperplasia** or **primary pigmented nodular adrenocortical disease (83%)**.
- We did **not find** case reports of cyclic Cushing's syndrome in patients with primary bilateral **macronodular adrenal** hyperplasia.

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Ectopic tumours

- **Pulmonary neuroendocrine tumours** were the most frequent (**31%**),
- **thymic neuroendocrine** tumours (**25%**).
- 11 cases of cyclic Cushing's syndrome were of **occult origin**, of which seven were probably ectopic in origin.
- In line with Meinardi and colleagues, we categorised six cases as unclassified referring to undescribed cases, possible cases of **hypothalamic disorders**, and cases of **empty sella syndrome**.

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Clinical presentation and comorbidities of cyclic Cushing's syndrome

- In cases with **very long trough** phases, clinical symptoms occurred with **peaks** of hypercortisolism and ceased with troughs. In patients with more ***rapid cycling***, clinical symptoms ***did not*** always ***resolve*** completely between peaks

Clinical presentation and comorbidities of cyclic Cushing's syndrome

- Weight gain (84 of 165 patients; **51%**, 95% CI 43–59),
- Moon face (69 of 135; **51%**, 42–60),
- Muscle weakness (75 of 165; **45%**, 38–53),
- Bruising (58 of 165; **35%**, 28–43), and
- Oedema (53 of 165; **32%**, 25–40) were frequently reported during hypercortisolaemic peaks.
- Hirsutism was described in 61 (**48%**, 95% CI 39–57), and
- Mmenstrual irregularities in 36 (**28%**, 21–37) of the 127 affected women.
-

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Clinical presentation and comorbidities of CCS in the **paediatric population**

- Growth retardation was reported in seven of 23 patients (**30%**, 95% CI 13–53)
- Overall, there was **no distinct** cyclic phenotype and Cushing-typical symptoms were present to **varying extents**.

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Comorbidities of cyclic Cushing's syndrome

- Hypertension (60%)
- Obesity (56%)
- Diabetes (31%)
- Osteoporosis (14%)
- Depression and emotional lability were also common in patients with cyclic Cushing's syndrome (38%)
- Headache (17%)
- Insomnia (7%)
- Thromboembolic complications were reported in 7 (3 DVT, 2 PTE, 1stroke, and one TIA) of 135 patients with cyclic Cushing's syndrome (**5%**)

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Potential mechanisms

Potential mechanisms

- Hypothalamic factors
- Positive feedback and negative feedback mechanisms
- Pituitary adenoma infarction, bleeding, and necrosis

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Hypothalamic factors of CCD

- Cyclic CD (CCD) may be primarily caused by **hypothalamic dysfunction.**
- The hypothalamus can produce serotonin (**5-HT**), and 5-HT plays a role in promoting the secretion of **ACTH**.
- **UFC** was significantly **decreased** in patients with CCD after taking the **5-HT antagonist cyproheptadine**, which simultaneously inhibits the periodic secretion of CCD.
- **Sodium valproate inhibits** the secretion of **CRH** by **increasing** the production of gamma-aminobutyric acid (**GABA**).

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Hypothalamic factors of CCS

- In some patients with **CCD**, the cortisol levels returned to normal after the **combined** use of the **dopamine D2 receptor** *agonizts* **cabergoline** and **sodium valproate**, but the effect was not reproducible when administered alone.

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Hypothalamic factors of CCS

- Therefore, the etiology of CCD may be related to periodic changes in substances that promote **ACTH secretion**, such as **CRH, dopamine**, and **GABA** released by the hypothalamus.

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Hypothalamic factors of CCD

- At the same time, the **recurrence rate** of CCD was **63%**, while the **remission rate** was **25%**. The recurrence rate of CCD is relatively high, while its remission rate is low **compared with classic CD** , which also suggests that CCD may be primarily caused by disruption in the hypothalamus.
- However, hypothalamic factors may only partially explain the etiology of CCD, not the periodicity of EAS and ACTH-independent CS.

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Positive feedback mechanisms

A glucocorticoid (GC)-driven positive feedback loop exists in some CCS patients, which is characterized by increased secretion of ACTH induced by endogenous or exogenous glucocorticoid.

- psychological stress
- metyrapone treatment

- In patients with EAS, pro-opiomelanocortin (POMC) mRNA expression and ACTH precursor secretion are increased after glucocorticoid treatment.

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Positive feedback mechanisms

- A recent multicenter study showed that **8.7%** of patients with **CD** may have a GC-driven **positive feedback system .**

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Negative feedback mechanisms:

- In contrast to the positive feedback loop, some researchers believe that the **fasciculate zone** of the adrenal gland and **pituitary adenoma** cells are sensitive to glucocorticoids.
- periodic ectopic CS:
- Bilateral adrenalectomy → **significantly increased** ACTH

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Pituitary adenoma infarction, bleeding, and necrosis

- Approximately **9.5–16.6%** of patients with pituitary adenomas experience infarctions, and some patients with CCD develop necrotic cells in pituitary adenomas.

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Diagnostics of CCS

Diagnostic methods of CCS and the advantages and disadvantages of different methods for diagnosing the disease.

	Use in CS	Advantages of diagnosing CCS	Disadvantages of diagnosing CCS
Qualitative diagnosis			
LNSC	Screening approach for CS	High sensitivity and specificity; noninvasive, convenient, and reproducible	It is not recommended for night workers, people whose salivary cortisol level was not sufficiently analyzed, and people with oral diseases.
UFC	Screening approach for CS	Good reproducibility	False-negative results may occur when the GFR is < 60 ml/min.
	Screening approach for CS	Inconsistent DST result may be CCS	May cause paradoxically elevated cortisol, misleading the diagnosis of CCS
UFCCR	Screening approach for CS	Good reproducibility; not affected by renal function	The sensitivity and specificity are not clear.
HCC	Diagnostic approach for CS	Currently, it is the only method that can reflect cortisol levels over the past few months or even years, and is extremely valuable for CCS diagnosis; Only requires one sample to determine whether cortisol secretion is cyclical.	The testing process is complicated, and many centers have not carried out this testing method.
Localization diagnosis			
ACTH	Used to differentiate between ACTH-dependent CS and ACTH-independent CS	NA	NA
CRH test	Used to differentiate between CD and EAS	NA	Many centers have not carried out this testing method.
HDDST	Used to differentiate between CD and EAS	Inconsistent DST result may be CCS	May cause paradoxically elevated cortisol, misleading the diagnosis of CCS.
DDAVP test	Used to differentiate between CD and EAS	Early detection of CCS and shortened diagnosis time	A unified standard has yet to be developed, and it is not recommended for routine diagnosis.
BIPSS	Gold standard for differentiating CD and EAS	For patients with CCS of unknown etiology, this is the gold standard for identifying pituitary and ectopic sources.	It needs to be measured during peak cortisol secretion; otherwise, false-negative results might be obtained; expensive; invasive
Imaging examination	Used to identify the etiology of CS	NA	Low sensitivity and prone to yielding false-negative results

ACTH, adrenocorticotrophic hormone; BIPSS, bilateral inferior petrosal sinus sampling; CRH, corticotropin-releasing hormone; DDAVP, desmopressin; DST, dexamethasone suppression test; GFR, glomerular filtration rate; HCC, hair cortisol concentration; HDDST, high-dose dexamethasone suppression test; LDDST, low-dose dexamethasone suppression test; LNSC, late-night salivary cortisol; NA, not available; UFC, urine free cortisol; UFCCR, late-night urinary free cortisol to creatinine ratio

Low-dose dexamethasone suppression tests

- The low-dose DST (LDDST), which includes the **overnight 1 mg** dexamethasone suppression test and the **longer 2-day low-dose** dexamethasone suppression test, helps the diagnosis of **classic CS**.
- However, the plasma and urinary free cortisol concentrations in patients with CCS during exacerbation may not be suppressed after treatment with dexamethasone, and a DST may lead to **paradoxical increases** in **cortisol** levels and negative results during remission; hence, the significance of this treatment is relatively low. DST is not recommended when CCS is suspected . However, if two DSTs performed at **different time** points showed **contradictory** results, CCS may exist

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Desmopressin test

- The DDAVP test is a valuable method for diagnosing CS and **stimulates ACTH** and **cortisol** production in most patients with CD. In :
- healthy individuals,
- alcoholism,
- depression,
- chronic kidney disease,
- poorly controlled diabetes,
- ACTH-independent CS, and
- ectopic CS
- do not cause elevations in the ACTH and cortisol levels

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Desmopressin test

- is not affected by drugs
- The DDAVP test may have unique advantages in the diagnosis of CCS.
- Alfonso et al. reported a patient with CCS whose repeat UFC, LNSC, plasma cortisol, and DST showed normal results; interestingly, the DDAVP test always yielded a positive result.
- Therefore, the DDAVP test may **shorten the time to diagnosis** CCS and allow patients to receive timely treatment . Notably, this method can also be used as an early marker for assessing the recurrence of CS as well as a long-term prognostic indicator for assessing the effect of surgery . However, since a unified standard has yet to be formulated, it is **not recommended for routine diagnosis .**

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Imaging examination

ACTH-dependent CS

- MRI
- 3-T MRI is increasingly used worldwide and may be effective in patients with negative or indeterminate imaging result.
- Approximately 15% of patients with EAS have no underlying tumor .
- **CT** or **MRI** examinations of the **neck**, **chest**, and **abdomen** are recommended.
- Since **most carcinoids** and other **neuroendocrine tumors** express **somatostatin receptors**, **octreotide receptor scintigraphy** can be used to diagnose EAS.
- If no tumor is found, positron emission (PET/CT) is recommended; **68Ga-DOTATATE PET/CT** is the first-line PET imaging modality that has higher accuracy compared with 18FDOPA-PET/CT

ACTH-independent CS

- For ACTH-independent CS,
- adrenal CT or MRI
- is recommended to identify the source of the tumor.

Diagnostics of CCS

- The diagnosis of CCS **remains challenging** and requires **close a follow-up of the patient** .
- Patients who fulfilled the following conditions were diagnosed with CCS:
- (1) The patient exhibited at least three peaks and two valleys in cortisol levels (the peaks should exceed the upper limit of normal) to diagnose CCS .
- (2) The patient had clinical symptoms of CS, which can spontaneously disappear or recur.
- (3) Imaging studies showed adrenal, pituitary, or ectopic lesions.
- (4) Patients did not use exogenous hormones and did not have simple obesity, autonomous cortisol secretion, pseudo-CS, or glucocorticoid-resistant syndrome

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Patients with Münchhausen’s syndrome

- who took **oral exogenous cortisol** to falsify the symptoms of the disease due to mental disorders, and who experienced intermittent cortisol elevations should receive clinical attention.

Long-term monitoring and follow-up

- Most patients with CCS have longer remission periods and require **long-term monitoring and follow-up**.
- Common monitoring methods include:
- late-night salivary cortisol (LNSC),
- 24-hour urine free cortisol (UFC),
- dexamethasone suppression test (DST),
- late-night urinary free cortisol to creatinine ratio (UFCCR),
- hair cortisol concentration (HCC), and
- dynamic tests.

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Treatment

- Surgery is the first line
- medical therapy
- radiation therapy,
- bilateral adrenalectomy

Surgical therapy

- The therapeutic effect of the initial **TSS** was **not** significantly **different** between the CCD and CD groups.
- However, many patients with CCD undergo **bilateral adrenalectomy** at a later stage, suggesting that persistent or recurrent cortisol hyperplasia may occur after TSS .
- The postoperative follow-up of CCS patients showed a **high recurrence rate (63%)** but a **low remission rate (25%)** compared with classical CS .
- Therefore, after surgical treatment, patients should be **monitored regularly** for recurrence.

Medical therapy

- Steroid synthesis inhibitors (ketoconazole, metyrapone, mitotane, etomidate),
- Somatostatin analogs (pasireotide),
- Dopamine agonizts (cabergoline), and
- Glucocorticoid receptor antagonists (mifepristone).
- **New drugs** currently under study for the treatment of CS include
- the **selective GR antagonist** relacorilant, retinoic acid, somatostatin-dopamine chimeric ligands, epidermal growth factor receptor inhibitors, cyclin-dependent kinase inhibitors, and heat shock protein 90 inhibitor .

Commonly used drugs for the treatment of cyclic Cushing's syndrome, the advantages of different drugs in the treatment of the disease, and the common side effects of the drugs.

Drug	Mechanism of action	Dose	Advantages of treating CCS	Side effects
Steroidogenesis inhibitors				
Ketoconazole	Inhibits StAR, CYP11A1, CYP11B1, and CYP17	400–1600 mg per day	For CCS, "block-and-replace" therapy can be used with steroid synthesis inhibitors.	Gastrointestinal complaints, hepatotoxicity and hypogonadism
Metyrapone	Potent inhibitor of CYP11B1 Weaker CYP17, CYP11B2, and CYP19	0.5–4.5 g per day	In ACTH-dependent CCS, the combination of metyrapone and glucocorticoids may prevent hypercortisolism.	Gastrointestinal complaints, hirsutism, hypertension, and hypokalemia
Mitotane	Inhibits StAR, CYP11A1, CYP11B1, CYP11B2, and 3β-HSD adrenolytic	3–5 g per day		Gastrointestinal complaints, gynecomastia, hepatotoxicity, adrenal insufficiency, and neurotoxicity
Etomidate	Inhibits StAR, CYP11A1, CYP11B1, CYP17	0.1–0.3 mg/kg/h intravenously		Gastrointestinal complaints, myoclonus
Osilodrostat	Inhibits StAR, CYP11B1, CYP11B2	4–14 mg per day		Gastrointestinal complaints, hypertension, hypokalemia fatigue, headache, and arthralgia
Pituitary tumor-directed drugs				
Pasireotide	SSTRs 5,2,3,1 Agonist, Decreases ACTH secretion and tumor cell proliferation	750–2400 ug per day subcutaneously injected	NA	Hyperglycemia, gastrointestinal complaints, and gallstones
Cabergoline	DR type 2 agonist, Decreases ACTH secretion	Up to 7 mg per week	May be a valuable treatment for occult CCS; cabergoline combined with sodium valproate may have a significant effect on CCS.	Gastrointestinal complaints, dizziness, and headache
Glucocorticoid receptor antagonists				
Mifepristone	Blocks PR and GR, preventing activation despite high cortisol levels	300–1200 mg per day	NA	Adrenal insufficiency, hypertension, edema, hypokalemia, and endometrial hyperplasia

Treatment

- Unlike CS, CCS must be **carefully controlled** with medication because **adrenal insufficiency** may be induced during the **nadir phase** of cortisol excess.
- For CCS patients, **“block-and-replace”** therapy can be administered using steroidogenic inhibitors.
- Steroid synthesis inhibitors are administered at higher initial doses to completely block endogenous cortisol secretion during exogenous glucocorticoid replacement therapy.

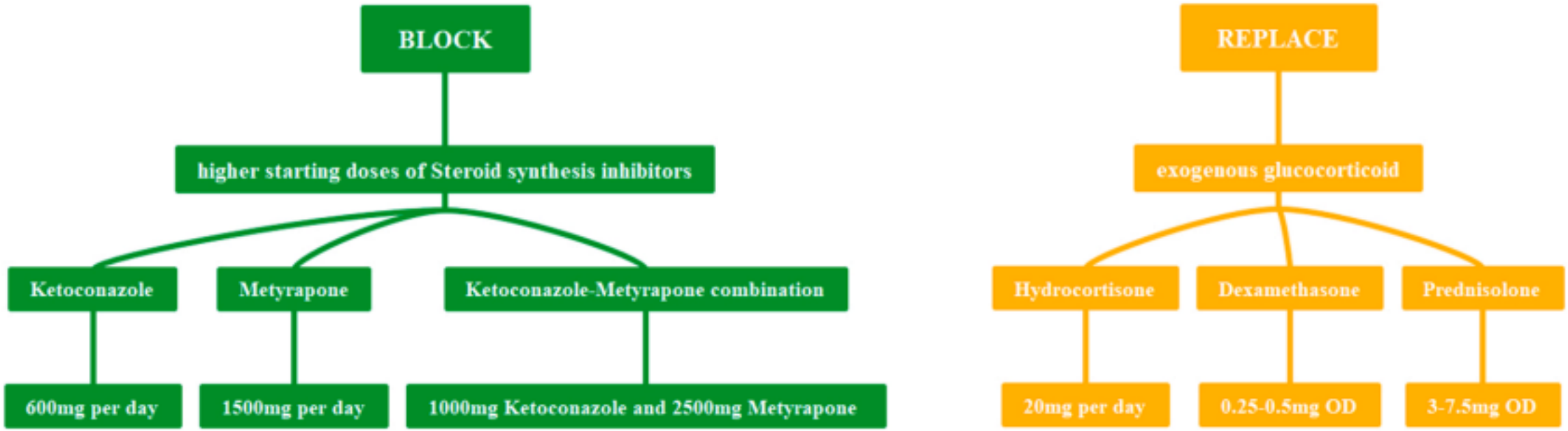

Fig. 3. "Block and replace" treatment approach for CCS.

Conclusion and prospects

- CCS is a rare disease and is characterized by cyclical secretion of cortisol, making it difficult to diagnose. Patients who showed conflicting results in two cortisol tests, who showed the same results on repeat clinical tests, who developed typical symptoms, and with normal laboratory test results, but showed opposite results on DST may be suspected of having CCS. Repeated UFC, LNSC, and plasma cortisol detection are all effective screening methods.

Conclusion and prospects

- Early diagnosis and timely and effective treatment are key to reducing the mortality rate of patients with CCS. Multidisciplinary individualized treatment methods, long-term followup, and timely treatment of complications can improve the prognosis of patients with CCS. This review provided new ideas regarding the pathophysiology of CCS as a scientific research and its treatment; moreover, findings of recent studies can improve the diagnosis and treatment of this disease. In the future, multi-center, large-sample research is required to assess the sensitivity and specificity of different diagnostic criteria and diagnostic methods. Further research is required to clarify the pathophysiology of CCS.

BIPSS in cyclic Cushing's syndrome

	PPV (ie, a true central source of ACTH)	NPV (ie, a true ectopic source of ACTH)	Sensitivity	Specificity
Hypercortisolism biochemically confirmed (n=27)	14/14 (100%, 77–100)	13/13 (100%, 75–100)	14/14 (100%, 77–100)	14/14 (100%, 77–100)
Hypercortisolism not biochemically confirmed (n=27)	5/12 (42%, 15–72)	11/15 (73%, 45–92)	5/9 (56%, 21–86)	11/18 (61%, 36–83)
Total (N=54)	19/26 (73%, 52–88)	24/28 (86%, 67–96)	19/23 (83%, 61–95)	24/31 (77%, 59–90)

Data are n/N (%, 95% CI). 54 BIPSS procedures performed in 42 patients with ACTH-dependent cyclic Cushing's syndrome (performed twice in 8 patients, and performed three times in 2 patients). 27 BIPSS procedures performed in 25 patients during hypercortisolism (performed twice in two patients). 27 BIPSS procedures performed in 24 patients during trough phases or unclear cortisolaemic states (performed twice in three patients). ACTH=adrenocorticotropic hormone. BIPPS=bilateral inferior petrosal sinus sampling. NPV=negative predictive value. PPV=positive predictive value.

The predictive value of BIPSS in patients with cyclic Cushing's syndrome

PSEUDO-CUSHING SYNDROME

- Clinically, patients with these physiologic forms of hypercortisolism **seldom** have the cutaneous (ie, easy bruising, thinning, and friability) or muscle (ie, proximal muscle atrophy and weakness) signs of Cushing syndrome .

- uptodate

Mitotane

- Mitotane presents a very **slow onset** of action; thus, its use is better suited in a “block and replace” regimen.
- It is best to use **hydrocortisone** instead of cortisol because longacting steroids (e.g. dexamethasone or prednisolone) can induce CS.
- This therapeutic approach requires close **monitoring of patients**’ **cortisol levels** to identify extreme elevations due to endogenous cortisol synthesis and exogenous glucocorticoid use.

- Studies have shown that the combination of **dexamethasone** and metyrapone can stimulate ACTH production through a glucocorticoid positive feedback loop. However, sufficient doses of metyrapone block the positive feedback loop of glucocorticoids; thus, endogenous cortisol levels do not increase.

cabergoline treatment alone

- The UFC and plasma ACTH levels were normal, complications of hypercortisolemia improved, and symptoms disappeared. Therefore, the use of cabergoline for the treatment of ectopic or occult CS may be a valuable therapeutic approach.

- Medical therapy includes steroid synthesis inhibitors (ketoconazole, metyrapone, mitotane, etomidate), somatostatin analogs (pasireotide), dopamine agonizts (cabergoline), and glucocorticoid receptor antagonists (mifepristone). New drugs currently under study for the treatment

- Most patients with CCS have longer remission periods and require **long-term monitoring and follow-up**.
- Common monitoring methods include:
- late-night salivary cortisol (LNSC),
- 24-hour urine free cortisol (UFC),
- dexamethasone suppression test (DST),
- late-night urinary free cortisol to creatinine ratio (UFCCR),
- hair cortisol concentration (HCC), and
- dynamic tests.

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Establishing the diagnosis of CCS

Late-night salivary cortisol

- In CD:
- sensitivity→ 95.8%
- specificity →93.4%
- The sensitivity of LNSC for diagnosing CCD was 88%, which was higher than that of UFC (12%)
- **Daily LNSC sampling** is recommended in patients with suspected CCS and LNSC helps determine the timing of bilateral inferior petrosal sinus venous sampling (BIPSS)

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Late-night salivary cortisol

- Measurement of LNSC is **not recommended** for:
- night workers
- people whose salivary cortisol levels were not sufficiently analyzed
- people with oral diseases

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24-h urine free cortisol

- Compared with plasma cortisol levels, cortisol levels are not affected by other diseases or drugs.
- Recent studies have reported that UFC measurement using **liquid chromatography-tandem mass spectrometry** (LC-MS/MS) improves the accuracy of screening for CS (97% sensitivity and 91% specificity) .
- In patients with clinical symptoms of CS but with normal urinary free cortisol levels, the urinary free cortisol levels should be **repeatedly measured** to rule out CCS. If the urinary free cortisol levels remain normal within **1 month**, the patient should be followed up for up to **1 year** and undergo repeat urinary free cortisol measurements

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Low-dose dexamethasone suppression tests

- The low-dose DST (LDDST), which includes the **overnight 1 mg** dexamethasone suppression test and the **longer 2-day low-dose** dexamethasone suppression test, helps the diagnosis of **classic CS**.
- However, the plasma and urinary free cortisol concentrations in patients with CCS during exacerbation may not be suppressed after treatment with dexamethasone, and a DST may lead to **paradoxical increases** in **cortisol** levels and negative results during remission; hence, the significance of this treatment is relatively low. DST is not recommended when CCS is suspected . However, if two DSTs performed at **different time** points showed **contradictory** results, CCS may exist

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Late-night urinary free cortisol to creatinine ratio

- **Free cortisol** is filtered by the **kidneys** and is greatly affected by **renal function**; false-negative results may occur when the GFR is < 60 ml/ min. UFCCR was positively correlated with UFC levels, and the upper limit of normal for the cortisol-to-creatinine ratio was 50 .
- Monitoring the UFCCR for **28 consecutive days** is recommended as a screening method for CCS. Some previous studies reported the detection of UFCCR levels in three CCS patients for 28 consecutive days, of whom two patients showed periodic cortisol secretion . The **good reproducibility** of UFCCR is a major advantage in the diagnosis of CCS.

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Hair cortisol concentration

- The cortisol concentration in a 1-cm hair segment reflects the cortisol levels within a **period of 1 month**; herefore, depending on the length of the hair, it is possible to detect the cortisol levels in the previous months or years.
- Measurement of HCC is currently the only method that can reflect the cortisol levels over the past few months or even years, and aids in the diagnosis of CCS

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Hair cortisol concentration in CS

- The sensitivity→ 86%
- and specificity →98%
- respectively, which were similar to the sensitivity and specificity of UFC and LNSC in screening for CS.
- **one sample**

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Hair cortisol concentration in CS

- Hair samples were obtained from the occipital region and cut as **close** as possible to the **skin**. Hair is stored in a cool plastic bag, and HCCs can stabilize for several months. **Enzyme-linked immunoassays** and **LC-MS** are the most commonly used preparative and analytical methods .
- In addition, age, sex, and hair changes (dyeing or bleaching) had **no significant effect** on hair cortisol levels, but hair cortisol levels were more influenced by psychoactive factors

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Establishing the cause of CCS

High-dose dexamethasone suppression test

- high-dose DST (HDDST)
- overnight 8 mg dexamethasone suppression
- 2-day dexamethasone suppression test of 2 mg every 6 h
- serum **cortisol levels** fell **below 52.7%** as the cutoff value for the diagnosis of CD, the sensitivity and specificity were 88% and 90%, respectively .
- However, in CCS, cortisol levels can vary widely on the day of the test, which can **mistakenly** lead to the **diagnosis of CCS**.

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Corticotropin-releasing hormone test

- Patients with **EAS** typically **do not respond** to the CRH test, whereas patients with CD have increased ACTH and cortisol levels.
- an **increase** in **ACTH ≥ 43%** **15 min after** **CRH** injection was the strongest predictor of CD, with a **sensitivity of 83%** and **specificity of 94%** . The sensitivity and specificity of the CRH test are similar to those of the HDDST .
- Some scholars have found that patients with **macroadenomas** have a **lower ACTH increase** after the CRH test than those with microadenomas .

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Desmopressin test

- The DDAVP test is a valuable method for diagnosing CS and **stimulates ACTH** and **cortisol** production in most patients with CD. In :
- healthy individuals,
- alcoholism,
- depression,
- chronic kidney disease,
- poorly controlled diabetes,
- ACTH-independent CS, and
- ectopic CS
- do not cause elevations in the ACTH and cortisol levels

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Desmopressin test

- is not affected by drugs
- The DDAVP test may have unique advantages in the diagnosis of CCS.
- Alfonso et al. reported a patient with CCS whose repeat UFC, LNSC, plasma cortisol, and DST showed normal results; interestingly, the DDAVP test always yielded a positive result.
- Therefore, the DDAVP test may **shorten the time to diagnosis** CCS and allow patients to receive timely treatment . Notably, this method can also be used as an early marker for assessing the recurrence of CS as well as a long-term prognostic indicator for assessing the effect of surgery . However, since a unified standard has yet to be formulated, it is **not recommended for routine diagnosis .**

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Bilateral inferior petrosal sinus sampling

- It is difficult to clinically identify the etiology of CCS, especially when no tumor is found on imaging examinations, and the localization of primary tumor remains challenging.
- The **primary tumor** remains **unknown** in approximately **13%** of patients with CCS.

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Bilateral inferior petrosal sinus sampling

- The BIPSS is the gold standard for differentiating CD from EAS. After **desmopressin** stimulation, the **central ACTH/peripheral ACTH** level was greater than **2**; after CRH stimulation, the central ACTH/peripheral ACTH level was greater than 3. These findings suggest that the etiology is in the pituitary gland, and the condition can be diagnosed as CD.
- Therefore, in CCS, the results of trough BIPSS may be misleading.

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Bilateral inferior petrosal sinus sampling

- Therefore, the BIPSS test should be performed at the **peak of cortisol** secretion to avoid false-negative results. BIPSS is recommended when the serum **cortisol level is > 10 µg/dL** or when the patient is in a phase of hypercortisolism, which is confirmed by measuring the **midnight salivary cortisol level** the previous night.

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IPSS

- The mild complications of BIPSS include
- tinnitus or
- ear pain (1–2%) and
- inguinal hematoma (2–3%),
- while its **serious complications** include
- nerve paralysis
- subarachnoid hemorrhage,
- thromboembolism

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Imaging examination

ACTH-dependent CS

- MRI
- 3-T MRI is increasingly used worldwide and may be effective in patients with negative or indeterminate imaging result.
- Approximately 15% of patients with EAS have no underlying tumor .
- **CT** or **MRI** examinations of the **neck**, **chest**, and **abdomen** are recommended.
- Since **most carcinoids** and other **neuroendocrine tumors** express **somatostatin receptors**, **octreotide receptor scintigraphy** can be used to diagnose EAS.
- If no tumor is found, positron emission (PET/CT) is recommended; **68Ga-DOTATATE PET/CT** is the first-line PET imaging modality that has higher accuracy compared with 18FDOPA-PET/CT

ACTH-independent CS

- For ACTH-independent CS,
- adrenal CT or MRI
- is recommended to identify the source of the tumor.

Treatment

- Similar to CS, CCS with an established etiology should be treated according to its cause. Surgery is the first line of treatment for CS. If surgical resection of the primary tumor is unsuccessful or infeasible, second-line treatment modalities such as medical therapy, radiation therapy, and bilateral adrenalectomy are used

Biochemical findings in cyclic Cushing's syndrome

- **Median plasma cortisol** concentrations were significantly higher in patients with cyclic Cushing's disease (**25·0 µg/dL**, range 2·7–290·0, IQR 18·5–34·9) compared with patients with *non-cyclic Cushing's disease* (**21·0** µg/dL, 5·1–67·1, 15·7–27·3; p=0·0339).

- They were also significantly higher in patients with **adrenal cyclic Cushing's** syndrome (**27·1 µg/dL**, 15·0–54·0, 18·8–42·9) compared with patients with non-cyclic adrenal Cushing's syndrome (**17·0** µg/dL, 3·2–32·0, 9·8–22·8; p=0·0027).

Diagnostic challenges in cyclic Cushing's syndrome: a systematic review
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Median UFC measurements

- were significantly **lower** in patients with **cyclic Cushing's disease (278·1** µg/24 h, range 4·7–4240·0, IQR 87·5–705·5) compared with patients with ***non-cyclic*** Cushing's disease (***426·0*** µg/24h, 29·0–10824·0, 269–827; p=0·0187).

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ACTH & late-night salivary cortisol (LNSC)

- There were **no significant differences in ACTH** between the two groups (cyclic Cushing's disease **70·4 pg/mL**, range 5·1–378·3, IQR 37·7–125·1 vs non-cyclic Cushing's disease **54·5 pg/mL**, 10·0–142·0, 37·0–83·0; **p=0·0755**) or in late-night salivary cortisol (**LNSC**) concentrations between the groups (cyclic Cushing's disease **7·6 ng/mL**, range 0·3–30·8, IQR 0·957–10·9375 vs non-cyclic Cushing's disease **8·3 ng/mL**, 0·3–306·1, 4·2–12·3; **p=0·4265**), but a ***trend of higher median plasma ACTH*** was observed in patients with cyclic Cushing's disease.

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Hypokalaemia

- Hypokalaemia was reported in 46 of 212 cases of cyclic Cushing's syndrome (**22%**, 95% CI 16–28).

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CCS

- The diagnosis can be unclear in patients with mild hypercortisolism or cyclic Cushing syndrome or when tests results are discrepant. In these patients, repeat testing after **3 to 6 months is appropriate.**

Imaging studies in cyclic Cushing's syndrome

- Imaging studies were reported in 142 cases of cyclic Cushing's syndrome, of which 91 (**64%,** 95% CI 56–72) were helpful or diagnostic.

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Imaging studies in cyclic Cushing's syndrome

- A **pituitary lesion** was found in 60 of the 88 patients with cyclic Cushing's disease who received imaging (**68%**, 57–78).
- Imaging was suggestive in six of 14 patients with **adrenal tumours** (**43%,** 18–71), and in 25 of 32 patients with **ectopic tumours** and documented imaging (**78%,** 60–91).

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Imaging studies in cyclic Cushing's syndrome

- **Three** patients with occult tumours and **five** patients with tumours of unclassified origin received imaging studies, which were **negative**. For the **58 cases** that described adrenal morphology, radiological **bilateral enlargement** was reported in 27 (**47%**, 33–60). Of these patients, 14 had *ectopic cyclic Cushing's syndrome*, eight had **cyclic Cushing's *disease***, three had *adrenal cyclic Cushing's* syndrome, one had occult cyclic Cushing's syndrome, and one had unclassified cyclic Cushing's syndrome.

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Imaging studies in cyclic Cushing's syndrome

Origin	cases of cyclic Cushing's syndrome	Imaging studies
helpful or diagnostic	91/142	64% (57–78)
pituitary lesion	60/88	(68%, 57–78)
adrenal tumours	6/14	(43%, 18–71)
ectopic tumours	25/32	(78%, 60–91)
occult tumours	3	neg
tumours of unclassified origin	5	neg
adrenal morphology	58	
radiological bilateral enlargement	27/58	(47%, 33–60)
	14	ectopic cyclic Cushing's syndrome
	8	cyclic Cushing's disease
	3	adrenal cyclic Cushing's syndrome
	1	occult cyclic Cushing's syndrome
	1	unclassified cyclic Cushing's syndrome.

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BIPSS in cyclic Cushing's syndrome

- In patients with ACTH-dependent hypercortisolism, BIPSS is used to distinguish between central (ie, pituitary) and non-central (ie, ectopic) tumour origins.146 This procedure is particularly useful when a central tumour source is suspected but MRI does not detect a pituitary adenoma.

BIPSS in cyclic Cushing's syndrome

	PPV (ie, a true central source of ACTH)	NPV (ie, a true ectopic source of ACTH)	Sensitivity	Specificity
Hypercortisolism biochemically confirmed (n=27)	14/14 (100%, 77–100)	13/13 (100%, 75–100)	14/14 (100%, 77–100)	13/13 (100%, 75–100)
Hypercortisolism not biochemically confirmed (n=27)	5/12 (42%, 15–72)	11/15 (73%, 45–92)	5/9 (56%, 21–86)	11/18 (61%, 36–83)
Total (N=54)	19/26 (73%, 52–88)	24/28 (86%, 67–96)	19/23 (83%, 61–95)	24/31 (77%, 59–90)

Data are n/N (%, 95% CI). 54 BIPSS procedures performed in 42 patients with ACTH-dependent cyclic Cushing's syndrome (performed twice in eight patients, and performed three times in two patients). 27 BIPSS procedures performed in 25 patients during hypercortisolism (performed twice in two patients). 27 BIPSS procedures performed in 24 patients during trough phases or unclear cortisolaemic states (performed twice in three patients). ACTH=adrenocorticotropic hormone. BIPPS=bilateral inferior petrosal sinus sampling. NPV=negative predictive value. PPV=positive predictive value.

Table 3: **The predictive value of BIPSS in patients with cyclic Cushing's syndrome**

BIPSS in cyclic Cushing's syndrome

	PPV (ie, a true central source of ACTH)	NPV (ie, a true ectopic source of ACTH)	Sensitivity	Specificity
Hypercortisolism biochemically confirmed (n=27)	14/14 (100%, 77–100)	13/13 (100%, 75–100)	14/14 (100%, 77–100)	14/14 (100%, 77–100)
Hypercortisolism not biochemically confirmed (n=27)	5/12 (42%, 15–72)	11/15 (73%, 45–92)	5/9 (56%, 21–86)	11/18 (61%, 36–83)
Total (N=54)	19/26 (73%, 52–88)	24/28 (86%, 67–96)	19/23 (83%, 61–95)	24/31 (77%, 59–90)

Data are n/N (%, 95% CI). 54 BIPSS procedures performed in 42 patients with ACTH-dependent cyclic Cushing's syndrome (performed twice in 8 patients, and performed three times in 2 patients). 27 BIPSS procedures performed in 25 patients during hypercortisolism (performed twice in two patients). 27 BIPSS procedures performed in 24 patients during trough phases or unclear cortisolaemic states (performed twice in three patients). ACTH=adrenocorticotropic hormone. BIPPS=bilateral inferior petrosal sinus sampling. NPV=negative predictive value. PPV=positive predictive value.

The predictive value of BIPSS in patients with cyclic Cushing's syndrome

ACTH or desmopressin or

- Analysis of stimulatory conditions revealed that corticotropin releasing hormone was used in 24 of 42 patients (57%, 95% CI 41–72) and desmopressin in five of 42 patients with cyclic Cushing's syndrome (12%, 4–26).
- The remaining 13 of 42 cases (31%, 18–47) either did not specify or only reported baseline gradients without stimulation.

Cycle characterisation in cyclic Cushing's syndrome

- Cycles varied in length—from a few days, to weeks, to months.
- Irregular intervals were more frequently reported (25 of 212 cases; 12%, 95% CI 8–17) than regular intervals (13 of 212; 6%, 3–10).
- The longest trough phases in between two hypercortisolaemic peaks were 3 years,4, 3·5 years, 4 years, and 3–5 years, during which the patients had repeatedly physiological biochemical findings. Spontaneous phases of hypocortisolism were described in seven of the 212 cases (3%, 95% CI 1–7%).

- Due to the absence of a uniform definition of a cycle, imprecise reporting of cases with challenges in clinical and biochemical follow-up

Treatment and outcome in cyclic Cushing's syndrome

- 114 of 143 patients with **cyclic Cushing's disease** (**80%**, 95% CI 72–86) had pituitary surgery, which was initially reported as successful in 79 patients (69%, 60–78).
- However, there was a **higher recurrence rate** among patients with **cyclic Cushing's disease** (24 of 79; **30%**, 21–42) than among patients with **noncyclic Cushing's disease** (54 of 275; **20%**, 95% CI 15–25; p=0·0465) during an overall mean follow-up time of 7·2 years (SD 7·0) for patients with cyclic Cushing's syndrome compared with 9·2 years (8·9) for patients with non-cyclic Cushing's syndrome (p=0·0113).

- Consequently, overall control rates were similar in patients with cyclic Cushing’s disease (103 of 143; 72%, 64–79) and patients with noncyclic Cushing’s disease (337 of 426; 79%, 75–83; p=0·0844) and in patients with adrenal cyclic Cushing’s syndrome (22 of 23; 96%, 78–100) and patients with non-cyclic adrenal Cushing’s syndrome (59 of 66; 89%, 79–96; p=0·6745).

therapy-induced remission

- There were significantly fewer cases of therapy-induced remission in patients with cyclic Cushing’s syndrome (94 of 165; 57%, 49–65) than in patients with non-cyclic Cushing’s syndrome (226 of 310; 73%, 95% CI 68–78; p=0·0007).

Cyclic ectopic Cushing’s syndrome,

- In patients with cyclic ectopic Cushing’s syndrome, control rates were slightly lower (24 of 36; 67%, 49–81) than in patients with noncyclic ectopic Cushing’s syndrome (10 of 10; 100%, 69–100; p=0·0439), but due to the small sample size this difference in rates should be interpreted with caution.

unnecessary surgeries

- Patients with cyclic Cushing’s syndrome had significantly more unnecessary surgeries (12 of 135 [eight pituitary surgeries performed in seven patients, two pulmonary surgeries, two unilateral adrenalectomies, and one thymectomy]; 9%, 5–15) than patients with non-cyclic Cushing’s syndrome (two of 139; 1%, 0–5; p=0·0055)

time to remission

- Overall, time to remission was significantly longer for patients with cyclic Cushing's syndrome (19 months, range 0·3–252·0) than for the reference cohort of patients with non-cyclic Cushing's syndrome derived from the LMU Munich hospital (2·1 months, 0·03–123·6; $p<0·0001$).

	Cyclic Cushing's syndrome					Non-cyclic Cushing's syndrome					p-value (cyclic *vs* non-cyclic Cushing's syndrome)
	Jahandideh et al (2018)[42]	Alexandraki et al (2009)[1]	Powel et al (2008)[69]	Single case reports and small case series[2–10,12–30,32,37–41,43,44,46–50,79–145]	Total	Jahandideh et al (2018)[42]	Alexandraki et al (2009)[1]	Powel et al (2008)[69]	LMU Munich longitudinal cohort*	Total	
Number of patients	38	30	9	135		167	171	25	139	502	..
Pituitary surgery in Cushing's disease	38/38 (100%, 91–100)	19/30 (63%, 44–80)	..	57/75 (76%, 65–85)	114/143 (80%, 72–86)	167/167 (100%, 98–100)	127/171 (74%, 67–81)	..	79/88 (90%, 82–95)	373/426 (88%, 84–91)	0·0272
Successful pituitary surgery in Cushing's disease	31/38 (82%, 66–92)	10/19 (53%, 29–76)†	..	38/57 (67%, 53–79)	79/114 (69%, 60–78)	136/167 (81%, 75–87)	79/127 (62%, 53–71)‡		60/79 (76%, 65–85)	275/373 (74%, 69–78)	0·4005
Relapse after successful pituitary surgery in Cushing's disease	10/31 (32%, 17–51)	4/10 (40%, 12–74)	..	10/38 (26%, 13–43)	24/79 (30%, 21–42)	36/136 (26%, 19–35)	12/79 (15%, 8–25)	..	6/60 (10%, 4–21)	54/275 (20%, 15–25)	0·0465
Pituitary radiation in Cushing's disease	4/38 (11%, 3–25)	1/30 (3%, 0–17)	..	12/75 (16%, 9–26)	17/143 (12%, 7–18)	27/167 (16%, 11–23)	..	..	5/88 (6%, 2–13)	32/255 (13%, 9–17)	1·0000
BADX in ACTH-dependent Cushing's syndrome	4/38 (11%, 3–25)	8/30 (27%, 12–46)	..	19/120 (16%, 10–24)	31/188 (16%, 12–23)	5/167 (3%, 1–7)	47/171 (27%, 21–35)	..	10/98 (10%, 5–18)	62/436 (14%, 11–18)	0·4645
Medical or adrenostatic treatment (ever)	14/38 (37%, 22–54)	2/30 (7%, 1–22)	..§	59/135 (44%, 35–53)	75/203 (37%, 30–44)	48/167 (29%, 22–36)	0/171 (0%, 0–2)	..§	29/139 (21%, 14–29)	77/477 (16%, 13–20)	<0·0001
Patients receiving unnecessary pituitary surgeries	0/38 (0%, 0–9)	0/19 (10%, 0–18)	..	7/65 (11%, 4–21)¶	7/122 (6%, 2–12)	0/167 (0%, 0–2)	0/127 (0%, 0–3)	..	2/81 (2%, 0–9)	2/375 (1%, 0–2)	0·0011
Patients receiving unnecessary surgeries	..	..	..	12/135 (9%, 5–15)	12/135 (9%, 5–15)	..	..	..	2/139 (1%, 0–5)	2/139 (1%, 0–5)	0·0055
Therapy-induced remission irrespective of tumour origin	..	14/30(47%, 28–66)‖	..§	80/135 (59%, 51–68)	94/165 (57%, 49–65)	..	114/171 (67%, 59–74)**	..§	112/139 (80%, 73–87)	226/310 (73%, 68–78)	0·0007
Therapy-induced remission in	..	14/30(47%,	..	45/75 (60%,	59/105 (56%,	..	114/171 (67%,	..	69/88 (78%,	183/259 (71%,	0·0100

	Cyclic Cushing's syndrome					Non-cyclic Cushing's syndrome					p-value (cyclic *vs* non-cyclic Cushing's syndrome)
	Jahandideh et al (2018)[42]	Alexandraki et al (2009)[1]	Powel et al (2008)[69]	Single case reports and small case series[2–10,12–30,32,37–41,43,44,46–50,79–145]	Total	Jahandideh et al (2018)[42]	Alexandraki et al (2009)[1]	Powel et al (2008)[69]	LMU Munich longitudinal cohort*	Total	
Therapy-induced remission in adrenal Cushing's syndrome	..	..	..§	13/14 (93%, 66–100)	13/14 (93%, 66–100)	..	..	..§	34/41 (83%, 68–93)	34/41 (83%, 68–93)	0·6639
Therapy-induced remission in ectopic Cushing's syndrome	..	..	..	21/36 (58%, 41–75)	21/36 (58%, 41–75)	..	..	..	9/10 (90%, 56–100)	9/10 (90%, 56–100)	0·1302
Therapy-induced remission or controlled irrespective of tumour origin	31/38 (82%, 66–92)	16/30 (53%, 34–72)††	9/9 (100%, 66–100)§	99/135 (73%, 65–81)‡‡	155/212 (73%, 67–79)	148/167 (89%, 83–93)	114/171 (67%, 59–74)**	25/25 (100%, 86–100)§	119/139 (86%, 79–91)	406/502 (81%, 77–84)	0·0278
Therapy-induced remission or controlled in Cushing's disease	31/38 (82%, 66–92)	16/30 (53%, 34–72)††	..	56/75 (75%, 63–84)	103/143 (72%, 64–79)	148/167 (89%, 83–93)	114/171 (67%, 59–74)**	..	75/88 (85%, 76–92)	337/426 (79%, 75–83)	0·0844
Therapy-induced remission or controlled in adrenal Cushing's syndrome	..	..	..	13/14 (93%, 66–100)	22/23 (96%, 78–100)	..	..	25/25 (100%, 86–100)§	34/41 (83%, 68–93)	59/66 (89%, 79–96)	0·6745
Therapy-induced remission or controlled in ectopic Cushing's syndrome	..	..	..	24/36 (67%, 49–81)	24/36 (67%, 49–81)	..	..	..	10/10 (100%, 69–100)	10/10 (100%, 69–100)	0·0439
Mean time to therapy induced remission, months	..	..	..	39·8 (SD 48·2, 0·3–252·0)§§	39·8 (SD 48·2, 0·3–252·0)§§	..	..	..	5·6 (SD 14·2, 0·03–123·6)¶¶	5·6 (SD 14·2, 0·03–123·6)¶¶	<0·0001
Median time to therapy-induced remission, months	..	..	..	19·0 (0·3–252·0, 8·85–48·0)§§	19·0 (0·3–252·0, 8·85–48·0)§§	..	..	..	2·1 (0·03 –123·6, 1·2–3·2)	2·1 (0·03–123·6, 1·2–3·2)	<0·0001
Total median time of follow-up, months	43·7 (2–128·2)	..	..	44·8 (0·3–252·0, 22·75–252·0)‖‖	..		..	..	37·6 (0–120·2, 7·23–63·47)	..	..

(Table 4 continued on next page)

	Cyclic Cushing's syndrome					Non-cyclic Cushing's syndrome					p-value (cyclic vs non-cyclic Cushing's syndrome)
	Jahandideh et al (2018)[42]	Alexandraki et al (2009)[1]	Powel et al (2008)[69]	Single case reports and small case series[2–10,12–30,32,37–41,43,44,46–50,79–145]	Total	Jahandideh et al (2018)[42]	Alexandraki et al (2009)[1]	Powel et al (2008)[69]	LMU Munich longitudinal cohort*	Total	
(Continued from previous page)											
Total mean time of follow-up, years	..	14·8 (8·8,*** 0–30)	..	5·0 (4·50·0–1·0)||||	7·2 (7·0)	..	14·0 (10·5,*** 0–52)	..	3·3 (2·8, 0·0–10·0)	9·2 (8·9)	0·0113

Data are N, n/N (%, 95% CI), mean (SD, range), or median (range, IQR). Cushing's disease was confirmed in patients with pathological ACTH-dependent hypercortisolism on the basis of histopathological diagnosis of a corticotroph tumour, positive immunostaining for ACTH, a well defined sellar lesion on imaging, clinical and biochemical remission following pituitary surgery, biochemical confirmation of ACTH-dependent Cushing's syndrome with a central gradient on BIPSS, or a combination of these indicators. ACTH=adrenocorticotropic hormone. BADX=bilateral adrenalectomy. *Patients treated at the LMU Munich hospital between 2012 and 2022. †Six patients with cyclic Cushing's syndrome were cured and four patients had recurrence after pituitary surgery, indicating an initial remission of ten patients.[1] ‡67 patients with non-cyclic Cushing's syndrome were cured and 12 had recurrence after pituitary surgery, indicating an initial remission of 79 patients.[1] §Five patients of unknown phenotype (ie, whether the patients had cyclic or non-cyclic Cushing's syndrome was not indicated) received adrenostatic therapy, and 32 of 34 patients of unknown phenotype were in remission.[63] ¶Eight unnecessary pituitary surgeries were performed in seven patients. ||Six patients were cured after pituitary surgery and eight patients had BADX, indicating a total of 14 patients with cyclic Cushing's syndrome in remission.[1] **67 patients were cured after pituitary surgery and 47 patients had BADX, indicating a total of 114 patients with non-cyclic Cushing's syndrome in remission.[1] ††Two patients received block-and-replace therapy, indicating a total of 16 patients with controlled cyclic Cushing's syndrome or cyclic Cushing's syndrome in remission.[1] ‡‡Including five patients with cyclic Cushing's syndrome who underwent spontaneous remission (two pituitary tumours, one ectopic tumour, one occult tumour, and one unclassified tumour). §§n=53. ¶¶n=112. ||||n=106. ***SD imputed from SE of the mean.

Table 4: **Differences in treatment and outcome between patients with cyclic and non-cyclic Cushing's syndrome**

Discussion

- Although cyclic Cushing’s syndrome is widely considered to be a rare form of Cushing’s syndrome, our literature search revealed an overall frequency of cyclicity of 14–18%. Some sources suggested cyclic Cushing’s disease to be discovered particularly frequently after pituitary surgery with a postoperative prevalence of 7–18%

- However, this prevalence might also be related to more regular postoperative biochemical testing for adrenal insufficiency. In primary pigmented nodular adrenocortical disease, cyclic Cushing’s syndrome could even account for one in four patients.69

- Likewise, patients with cyclic Cushing’s syndrome should receive the same comorbidity screening and appropriate treatment as patients with non-cyclic Cushing’s syndrome.

- The Endocrine Society practice guidelines suggest UFC and LNSC measurements rather than dexamethasone suppression tests in patients suspected of having cyclic Cushing’s syndrome.
- Although UFC was measured and reported in almost all cases, data on LNSC were scarce.

- When investigated during a trough phase or undetermined cortisolaemic state, ACTH secretion from healthy pituitary corticotroph cells might not be fully suppressed.

- When investigated during a trough phase or undetermined cortisolaemic state, ACTH secretion from healthy pituitary corticotroph cells might not be fully suppressed. In a patient with ectopic Cushing’s syndrome, unsuppressed physiological ACTH could lead to a high central-to-peripheral ACTH gradient, falsely indicating
- a pituitary source of ACTH hypersecretion.

- ترشح ACTHاز سلول های کورتیکوتروف هیپوفیز سالم ممکن است به طور کامل سرکوب نشود، زمانی که در طول یک فاز پایین یا وضعیت کورتیزولمی نامشخص بررسی شود. در یک بیمار مبتلا به سندرم کوشینگ نابجا، ACTHفیزیولوژیکی سرکوب نشده می تواند منجر به شیب بالای ACTHمرکزی به محیطی شود، که به اشتباه منبع هیپوفیز بیش از حد ترشح ACTHرا نشان می دهد.

- When compared with patients with non-cyclic Cushing’s syndrome, imaging was similarly useful in identifying tumour origins in patients with Cushing’s disease and ectopic Cushing’s syndrome, but less useful than in patients with adrenal Cushing’s syndrome. This difference is probably due to higher rates of bilateral hyperplasia and unilateral adenoma in patients with non-cyclic Cushing’s syndrome.

- We found a significantly higher use of medical or adrenostatic therapy in patients with cyclic Cushing’s syndrome. This therapy might be of particular use in treating occult or ectopic cyclic Cushing’s syndrome, as the time to tumour identification might be longer. In cases with more rapid cycling or when regular control visits are not feasible, we suggest a block-and-replace approach to avoid adrenal insufficiency due to unpredictable cycle intensity and the possibility of spontaneous hypocortisolism.

- Our literature search showed that a substantial number of patients do not have complete remission of clinical symptoms between hypercortisolaemic peaks.

- As three large case series1,42,69 accounted for 77 (36%) of the total 212 included cases of cyclic Cushing’s syndrome, there might have bee
- We are aware that some of the significantly different outcomes between patients with cyclic Cushing’s syndrome and non-cyclic Cushing’s syndrome, such as time to remission, were partly due to the large heterogeneity from the literature-derived cases reported n considerable reporting bias.

The pathophysiological mechanisms

- influence of some neurotransmitters
- hypothalamic dysregulation, and feedback mechanisms

- Atkinson and colleagues85,126 proposed that cyclic Cushing’s syndrome might be an exaggeration of physiological cyclical variation in cortisol concentration.
- This theory is supported by studies reporting variations in steroid secretion in patients with non-cyclic Cushing’s syndrome and subclinical Cushing’s syndrome.

- On the other hand, the long trough phases lasting several years observed in some patients with cyclic Cushing’s syndrome is an argument against the exaggeration theory.

- Regardless, since long and possibly even permanent spontaneous remission has been described in cyclic Cushing’s syndrome, further characterisation of these patients has the potential to substantially contribute to the understanding of the development and disease activity of, and even cure for, Cushing’s syndrome.

Definitions of sensitivity, specificity, and positive and negative predictive values

	Disease present	Disease absent
Test positive	**A**	**B**
Test negative	**C**	**D**
Sensitivity = A ÷ (A + C)		
Specificity = D ÷ (B + D)		
Positive predictive value = A ÷ (A + B)		
Negative predictive value = D ÷ (C + D)		

PSEUDO-CUSHING SYNDROME

- Clinically, patients with these physiologic forms of hypercortisolism **seldom** have the cutaneous (ie, easy bruising, thinning, and friability) or muscle (ie, proximal muscle atrophy and weakness) signs of Cushing syndrome .

- uptodate

Testing for non-neoplastic hypercortisolism (pseudo-CS)

- Psychiatric disorders
- alcohol use disorder
- polycystic ovary syndrome, and
- obesity
- may activate the hypothalamic-pituitary-adrenal (HPA) axis.
- Furthermore, concomitant medications could result in steroid cross-reactivity or otherwise interfere with laboratory test results.

Consensus on Diagnosis and Management of Cushing's Disease: 2 A Guideline Update
Version of Record: https://www.sciencedirect.com/science/article/pii/S2213858721002357
Manuscript_817242ea1c0e1c57ff519f87a97b0354

Testing for non-neoplastic hypercortisolism (pseudo-CS)

- Such patients also may have 208 concomitant features of CS that are common in the general population (e.g., weight gain) that 209 lead to biochemical screening. DST, LNSC, and UFC may all show positive (abnormal) results in these patients with non-neoplastic clinical hypercortisolism, or so-called pseudo-CS.

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Testing for non-neoplastic hypercortisolism (pseudo-CS)

- However, these abnormal results tend to be mildly elevated; UFC is almost always within 3-fold of normal. The combined LDDT-CRH (Dex-CRH) test, LDDT, or the desmopressin test may be able to distinguish between ACTH-dependent CS and pseudo-CS.
- Utility of the Dex-CRH test in this setting is based on the assumption that only patients with ACTH-dependent CS will show a cortisol response to CRH after dexamethasone suppression.

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Testing for non-neoplastic hypercortisolism (pseudo-CS)

- However, test reliability may differ due to different protocols, various **ovine** or **human CRH doses**, characteristics of **cortisol and ACTH assays**, and **patients** (e.g., degree of hypercortisolism, adrenal versus pituitary CS, and underlying conditions). Use of the desmopressin test is based on the finding that ACTH-secreting adenomas express vasopressin V1b (V3) receptors, producing a rise in plasma ACTH after desmopressin injection. The desmopressin test has a high specificity for CD , is less complex and expensive than the Dex -CRH test, but both have shown good diagnostic performance in distinguishing CS from pseudo CS in some studies; when both tests are done, they showed excellent agreement.

IPSS

- 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-CS **overlaps** that seen in patients with CD (HQ, SR). In classical cyclic CD or in patients with unpredictable fluctuating cortisol levels, dynamic testing and localization testing, including IPSS, should be preceded by a confirmatory LNSC, DST, or UFC to document that the patients are in the active phase.

Consensus on Diagnosis and Management of Cushing's Disease: 2 A Guideline Update

Ruling out pseudo-CS

- We recommend considering the patient's clinical history, particularly the duration of symptoms, and repeating testing to avoid implementing inappropriate treatment if CS is not present (LQ, DR).
- . 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 levels (LQ, DR). Standard diagnostic testing is unreliable in this population.
- LDDT or serial LNSCs over time correlate with the clinical picture (LQ, DR). 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 center with measurement of dexamethasone levels is advised (MQ, SR),54 264 as is 265 cortisol cut-off adjustments in very obese patients. Ovine CRH is not presently available in the
- United States, Canada, Brazil, Argentina, Mexico and some other countries

During petrosal sinus sampling

- Desmopressin has been used in place of CRH to perform petrosal sinus sampling in small series. There are differences of opinion about when to use this test clinically.
- Many clinicians → CRH
- another approach → Desmopressin
- combined CRH and desmopressin testing
- However, desmopressin (alone or in combination with CRH) during inferior petrosal sinus sampling may, on occasion, yield a false-positive diagnosis of Cushing disease.
- Some studies and meta-analyses have found that the ACTH response to desmopressin during inferior petrosal sinus sampling had a sensitivity of 95 to 99 percent for the diagnosis of Cushing disease and was equivalent or even superior to CRH

- It has been suggested that desmopressin testing and the high-dose dexamethasone suppression test performed on separate occasions can reduce the need for petrosal sinus sampling [60]. A noninvasive algorithm to avoid petrosal sinus sampling has been proposed involving peripheral desmopressin and CRH testing in conjunction with pituitary and extensive whole-body imaging; this approach has the potential to avoid 47 percent of the current indications of bilateral inferior petrosal sinus sampling.

- Desmopressin, a vasopressin analogue, stimulates corticotropin secretion in patients with Cushing disease and in some patients with neuroendocrine tumors.
- In contrast, desmopressin does not meaningfully stimulate corticotropin secretion in healthy subjects or in those with nonneoplastic, physiological hypercortisolism.
- Dexamethasone-CRH testing (patients take 0.5 mg of dexamethasone every 6 hours for 2 days and **2 hours after the last dose of** dexamethasone **CRH** is administered **intravenously**) can distinguish **Cushing disease** from **nonneoplastic hypercortisolism**.

1 mg Overnight Dexamethasone Suppression Test

- The 1 mg overnight dexamethasone suppression test (ODST) protocol is associated with high diagnostic accuracy as a first line test to confirm the presence of hypercortisolism, except in pregnancy, possible cyclical Cushing syndrome, and epilepsy (if antiepileptics enhance dexamethasone suppression) [1]. Cut-offs will need to be appropriate for local cortisol method, but stringent thresholds are recommended .
- Pitfalls in the Diagnosis and Management of Hypercortisolism (Cushing Syndrome) in Humans; A Review of the Laboratory Medicine Perspective Kade C. Flowers 1 and Kate E. Shipman 1,2,

Serotonin (5-Hydroxyindole Acetic Acid)

- Cushing syndrome has been described in cases of a type of NET, carcinoid; carcinoid tumours are the most common cause of **cyclical Cushing syndrome** due to **ectopic ACTH secretion** . Carcinoid tumours produce biogenic amines, of which serotonin is used as a screening tool. The metabolite of serotonin, 5-hydroxyindole acetic acid (5HIAA), is widely measured in 24 h urine collections. However, specificity and sensitivity are limited . Platelet serotonin is not affected by diet, unlike urine 5HIAA, and is more sensitive but not widely available. Again, the use in Cushing screening is therefore negligible, but in suspected/proven carcinoid tumours, it may be a useful marker to monitor treatment success.

- Pitfalls in the Diagnosis and Management of Hypercortisolism (Cushing Syndrome) in Humans; A Review of the Laboratory Medicine Perspective Kade C. Flowers 1 and Kate E. Shipman 1,2,

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- The most impressive presentations of cyclic Cushing’s syndrome consist of case reports in which the cyclicity of cortisol hypersecretion follows a pseudorhythm with multiple episodes of identical length,3 or in which several years might pass between cycles.

- Diagnostic challenges in cyclic Cushing’s syndrome: a systematic review
- www.thelancet.com/diabetes-endocrinology Vol 11 August 2023