
IN THE NAME of GOD

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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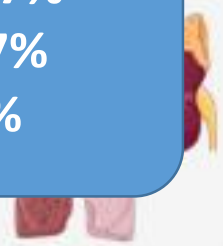
Cyclic Cushing's Syndrome

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.

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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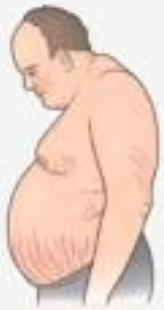

Cortisol secretion patterns

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.

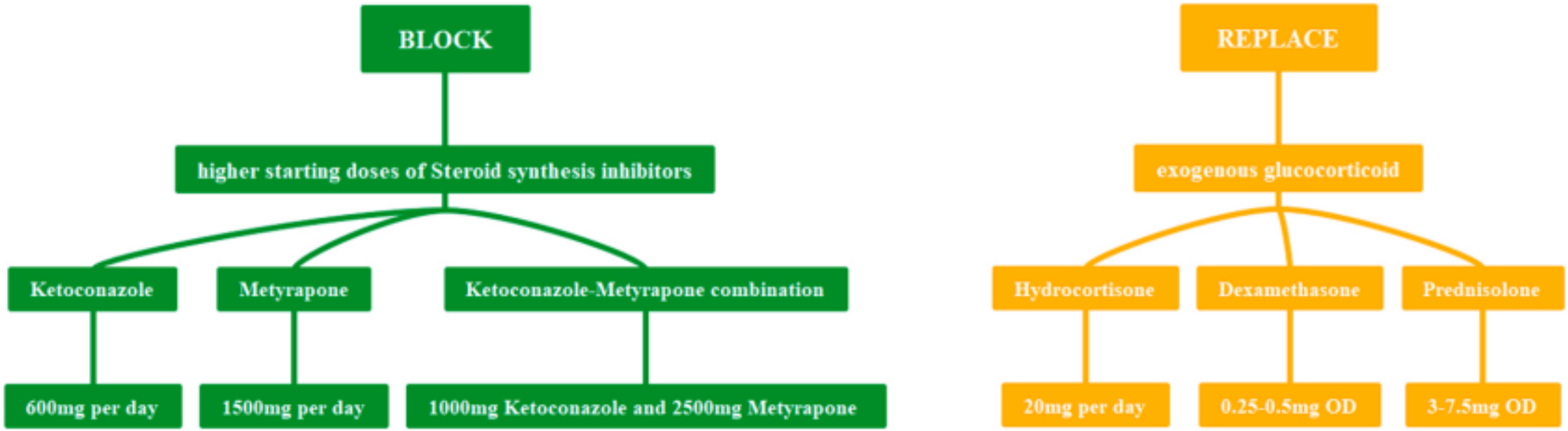

Fig. 3. "Block and replace" treatment approach for CCS.

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.