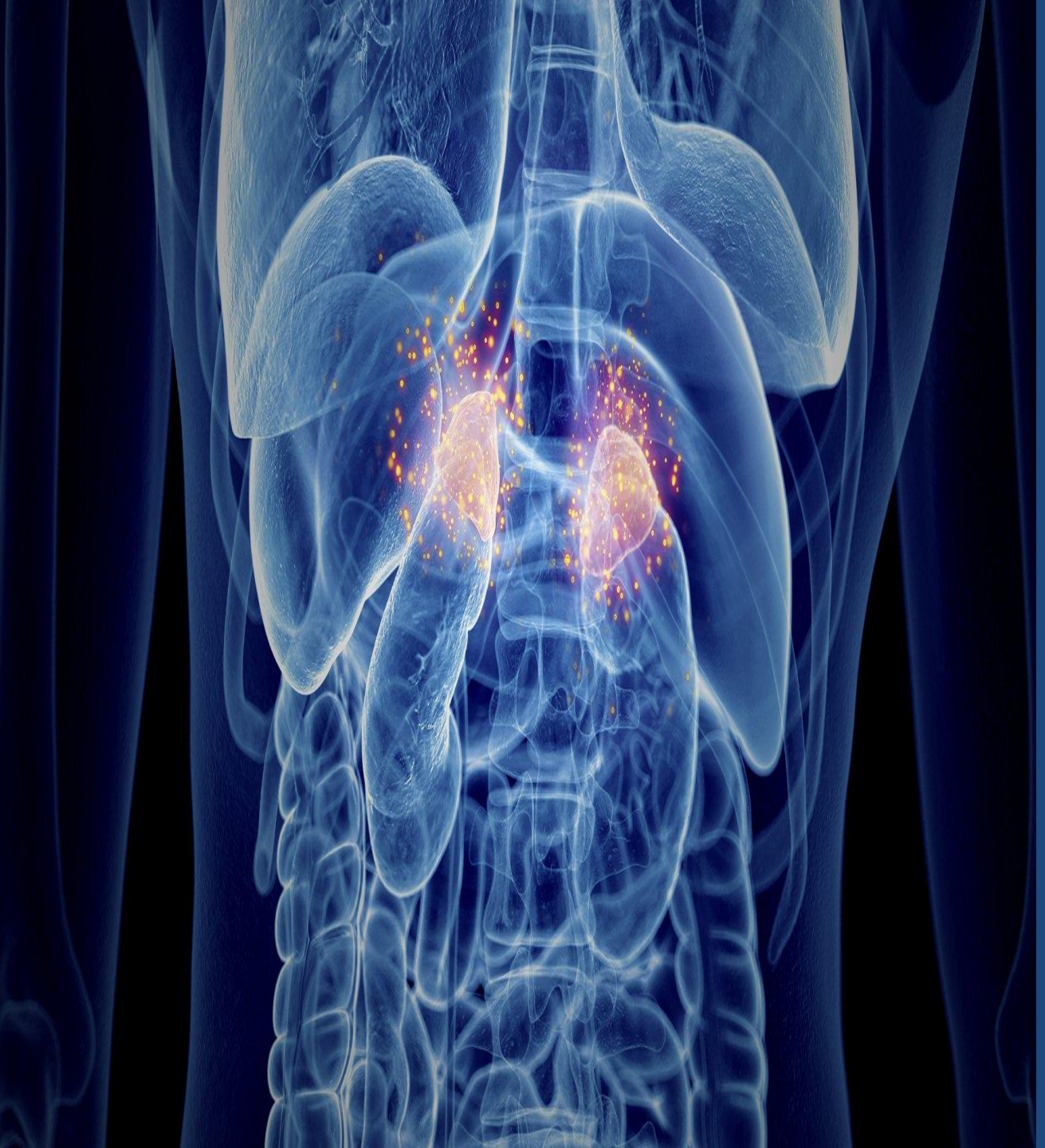

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Clinical Practice Guideline

ENDOCRINE SOCIETY

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European Society of Endocrinology and Endocrine Society Joint Clinical Guideline

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DIAGNOSIS AND THERAPY OF GLUCOCORTICOID-INDUCED ADRENAL INSUFFICIENCY

Introduction

- Virtually **every discipline of medicine applies glucocorticoids** via multiple modes of administration (including **oral, inhaled, intranasal, intra-articular, topical, and intravenous**), and frequently for prolonged duration.

- Suppression of the **hypothalamic-pituitary-adrenal (HPA) axis** is an inevitable effect of **chronic** exogenous glucocorticoid therapy and **recovery of adrenal function varies greatly amongst individuals**.

- **Glucocorticoid-induced adrenal insufficiency** necessitates **careful education and management**, and in the rare cases of **adrenal crisis, prompt diagnosis and therapy .**

- Considering the **widespread use of glucocorticoids** and the **risk for glucocorticoid-induced adrenal insufficiency**, the present **clinical practice guideline provides guidance on this clinically relevant condition to aid the endocrinology specialists, as well as general practitioners and other specialists involved in the care of these patients.**

Adverse Effects of Long-term Glucocorticoid Therapy

- While glucocorticoids are highly effective agents in the **treatment of autoimmune and inflammatory disorders**, they can **cause adverse reactions, particularly when administered at high doses and/or for a prolonged period.**
- However, even relatively **low dose** (in the range of **physiologic daily dose** equivalent), **long-term** glucocorticoid therapy is linked to a range of **adverse outcomes.**
- For instance, a **British** cohort study involving **9387 patients** with rheumatoid arthritis observed over a median of 8 years (with an average **prednisone** dosage of **5.8 mg/day for approximately 9.5 months**) exhibited elevated rates of conditions such as **diabetes, osteoporosis, fractures, hypertension, thrombotic events, gastrointestinal complications, and increased mortality,** compared to those not treated with glucocorticoids.

Any glucocorticoid dose above the physiologic daily dose equivalent can potentially lead to suppression of the HPA axis.

The **degree and persistence of HPA axis suppression** after cessation of glucocorticoid therapy are **dependent on overall exposure, which, amongst other factors, is determined by potency of the glucocorticoid (Table 1), glucocorticoid dose, length of therapy, and individual susceptibility.**

Notably, **any route of administration** has the **potential of HPA axis suppression,** including **oral, topical, inhaled, intra-nasal, intravenous and intra-articular administration.**

- **While tapering glucocorticoids** within the supraphysiologic dose range, patients can develop **glucocorticoid withdrawal syndrome**, which manifests with clinical features **similar to those of adrenal insufficiency**.

- However, **symptoms due to adrenal insufficiency are much more likely** to develop **when overall total daily glucocorticoid dose is below physiologic levels, or levels required for an adequate stress response.**

Table 1. Pharmacologic characteristics of commonly prescribed systemic glucocorticoids (19-23)

Glucocorticoids	Approximate equivalent dose[a]	Glucocorticoid potency (relative to hydrocortisone)[a, b]	Plasma half-life (min)[a, c]	Biological half-life (hours)[a]	Therapeutic indications
Short-acting glucocorticoids with lower potency					
Hydrocortisone	20 mg	1.0	90-120	8-12	Adrenal insufficiency replacement
Cortisone acetate	25 mg	0.8	80-120	8-12	Adrenal insufficiency replacement
Deflazacort	7.5 mg	1.0	70-120	Not defined	Duchenne muscular dystrophy
Intermediate-acting glucocorticoids with moderate potency					
Prednisone	5 mg	4.0	60	12-36	Anti-inflammatory, immunosuppressant; Adrenal insufficiency replacement
Prednisolone	5 mg	4.0	115-200	12-36	Anti-inflammatory, immunosuppressant; Adrenal insufficiency replacement
Triamcinolone	4 mg	5.0	30	12-36	Anti-inflammatory, immunosuppressant
Methylprednisolone	4 mg	5.0	180	12-36	Anti-inflammatory, immunosuppressant
Long-acting glucocorticoids with highest potency					
Dexamethasone	0.5 mg	30-60	200	36-72	Anti-inflammatory, immunosuppressant; Usually reserved for short-term use in severe, acute conditions
Betamethasone	0.5 mg	25-40	300	36-72	Anti-inflammatory, immunosuppressant; Usually reserved for short-term use in severe, acute conditions

Epidemiology of Glucocorticoid-induced Adrenal Insufficiency and Associated Morbidity and Mortality

A meta-analysis of the risk of developing biochemical glucocorticoid-induced **adrenal insufficiency** stratified by glucocorticoid route of administration showed pooled percentages of **4.2%** (95% CI 0.5-28.9) **for nasal administration**, **48.7%** (95% CI 36.9-60.6) **for oral use**, and **52.2%** (95% CI 40.5-63.6) **for intra-articular administration.**

The risk also varied when stratified for the **underlying disease and increased with higher dose** (**low dose 2.4%** (95% CI 0.6-9.3) **to high dose 21.5%** (95% CI 12.0-35.5)) and **longer treatment duration** (**1.4% (95% CI 0.3-7.4) (<28 days)** to **27.4% (95% CI 17.7-39.8) (>1 year))** in patients with asthma.

Since an estimated minimum of **1% of adult populations** (*United States and United Kingdom*) use oral glucocorticoids at any given time , this would imply **several million people are at risk of developing glucocorticoid-induced adrenal insufficiency** in these countries alone.

Definitions

Glucocorticoid exposure via oral administration that poses risk for adrenal insufficiency, **is expected to at least exceed both of the following thresholds:**

- **Duration of glucocorticoid therapy** to pose risk for adrenal insufficiency—**3-4 weeks, or greater**
- **Dose of glucocorticoid therapy** to pose risk for adrenal insufficiency—**any dose greater than daily hydrocortisone equivalent of 15-25 mg (4-6 mg prednisone or prednisolone, 3-5 mg methylprednisone, 0.25-0.5 mg dexamethasone)**

The following defined terms will be used in the remainder of these guidelines:

- **Physiologic daily dose equivalent**: Daily glucocorticoid dose equivalent to average daily cortisol production **(15-25 mg hydrocortisone, 4-6 mg prednisone or prednisolone, 3-5 mg methylprednisone, 0.25-0.5 mg dexamethasone).**

- **Endogenous production of cortisol** is estimated to be **9-10 mg/day.**

- **Supraphysiologic glucocorticoid therapy**: Any dose greater than physiologic daily dose equivalent (see above)

- **Short-term glucocorticoid therapy**: Any glucocorticoid therapy of less than 3-4 weeks duration

- **Long-term glucocorticoid therapy:** Glucocorticoid therapy greater than 3-4 weeks duration with glucocorticoid doses **greater than physiologic daily dose** equivalent of hydrocortisone.

- **Glucocorticoid taper**: Taper of glucocorticoid therapy dose, **initially guided by the management of the underlying disease (= therapeutic taper)**, and later by the **management of glucocorticoid withdrawal and adrenal insufficiency (= endocrine taper)**

- **Glucocorticoid withdrawal syndrome**: Symptoms experienced when lowering glucocorticoid dose within the supraphysiologic glucocorticoid dose range, that are **not due to the underlying disease** for which the glucocorticoids were initially prescribed for and per definition **not due to untreated adrenal insufficiency**, as the total glucocorticoid daily dose is **still supraphysiologic**

Aims

The **overall purpose of this guideline** is to provide

clinicians with practical guidance on the evaluation of adrenal function of adult patients with long-term supraphysiologic glucocorticoid therapy and for supplementation therapy in case of glucocorticoid- induced adrenal insufficiency.

Recommendations

1. General recommendations for glucocorticoid therapy of non-endocrine conditions and recommendations regarding patient education

R 1.1—We recommend that, in general, patients on, or tapering off glucocorticoids for non-endocrine conditions do not need to be evaluated by an endocrinology specialist.

- **Rationale**

- Despite their efficacy as anti-inflammatory and immunosuppressive agents, **chronic use of glucocorticoids can induce manifestations of Cushing syndrome**, along with **concomitant central and later permanent adrenal insufficiency** (suppression of the entire HPA axis) .
- For this reason, clinicians prescribing glucocorticoids for non-endocrine reasons are advised to employ **the lowest effective dose and duration of therapy and consider tapering glucocorticoid doses** when treatment is no longer necessary for the underlying condition.

- When prescribing clinicians decide that **glucocorticoid therapy is no longer required**, they should **educate their patient on methods to taper the dose, symptoms of adrenal insufficiency and appropriate responses, and proceed to wean the dose** (Table 2).

R 1.2—We recommend that clinicians who implement treatment with glucocorticoids educate patients about various endocrine aspects of glucocorticoid therapy. (Good clinical practice)

- **Rationale**

- Clinicians prescribing **long-term supraphysiologic glucocorticoid therapy** should actively **educate their patients about the potential development of adverse manifestations associated with exogenous Cushing syndrome** during extended use.

- Furthermore, patients need to be **informed about the risks of adrenal insufficiency,** especially **when tapering glucocorticoid medication below the physiologic daily dose equivalent** (see Definitions section).

- Clinicians should also provide comprehensive guidance on the **importance** of **stress dosing with glucocorticoids**. (see recommendation 3.1).

- Lastly, all patients initiating a glucocorticoid taper should be **educated on the possibility of glucocorticoid withdrawal syndrome** .
- The symptoms of **glucocorticoid withdrawal** have substantial **overlap with symptoms of adrenal insufficiency** and in some cases a disease flare, and can impede the tapering of glucocorticoids (see recommendation 2.3).
- **Anticipation of these potential symptoms** can **increase awareness and minimize the need for urgent care.**

Table 2. Overview of topics prescribing clinicians should discuss with patients when prescribing oral glucocorticoids

Considerations	Eligible patients	Timing	Comments
Risk for developing exogenous Cushing syndrome	All patients on long-term supraphysiologic glucocorticoid therapy	At the time of initiation	There are many sequelae of exogenous Cushing syndrome. Patients should be educated on the most common and clinically significant, including weight gain, sarcopenia, hyperglycemia, hypertension, bone demineralization
Risk for developing chronic adrenal insufficiency			Even transient adrenal insufficiency requires education to raise awareness for the need to stress dose when appropriate
Education on stress dosing strategies Education on injectable emergency glucocorticoid administration	Patients on long-term supraphysiologic glucocorticoid therapy who have reduced dosing to physiologic, or subphysiologic, levels	At least at the time when dosing approaches a physiologic range	Dedicated education should be provided to prepare patients with confirmed, or likely, adrenal insufficiency for routine and emergent stress dosing
Glucocorticoid withdrawal syndrome	Patients on long-term supraphysiologic glucocorticoid therapy who are ready to begin tapering the dose	At the time glucocorticoid tapering begins	Some patients on long term supraphysiologic glucocorticoid therapy experience symptoms as the doses are tapered

R 1.3—We recommend that patients on glucocorticoid therapy have access to current up-to-date and appropriate information about different endocrine aspects of glucocorticoid therapy. (Good clinical practice)

- **Rationale**

- **Empowering patients** with **knowledge of the benefits and risks of glucocorticoid therapy is critical .**

- We recommend the **inclusion of at least one family member or primary caregiver** in all education sessions.

- Patient **education and empowerment** to **adjust glucocorticoid doses according to stressors** are essential to prevent severe symptoms of adrenal insufficiency and adrenal crisis .

- **Poor disease knowledge and lack of awareness** of **adrenal insufficiency subtype diagnosis** were associated with **higher rates of adrenal crisis.**

- **Standardized patient education programs** for patients and their relatives proved to be useful for sustainably improving the level of knowledge regarding the **prevention of adrenal crisis**, as well as **self- confidence** in dealing with the disease

- The **risk for developing adrenal insufficiency** and the **potential for adrenal crisis during glucocorticoid treatment and taper** is **low** but **increases** with the cumulative number of risk factors including glucocorticoid **potency, administration route, dose and treatment duration (Table 3).**

Table 3. Risk factors for developing adrenal insufficiency, and susceptibility to adrenal crisis, during glucocorticoid therapy and withdrawal from therapy

Factors	Risk for adrenal insufficiency and crisis		
	Low	Moderate	High
Glucocorticoid potency	Hydrocortisone Cortisone acetate Deflazacort	Prednisone Prednisolone Methylprednisolone Triamcinolone	Dexamethasone Betamethasone Fluticasone
Administration Route	Nasal Topical Ophthalmic	Inhaled	Systemic (oral, intramuscular, I intravenous) Intra-articular Concurrent use of differently aadministered glucocorticoid
Dose	Low	Medium	High
Duration of use	<3-4 weeks	3-4 weeks-3 months	>3 months
Body Mass Index (64)	Normal	Overweight	Obese
Age (65)	Younger adults		Older adults

2. Recommendations regarding taper of systemic glucocorticoid therapy for non-endocrine conditions, diagnosis and approach to glucocorticoid-induced adrenal insufficiency, and glucocorticoid withdrawal syndrome

R 2.1—We suggest not to taper glucocorticoids in patients on short-term glucocorticoid therapy of <3-4 weeks, irrespective of the dose.

In these cases, glucocorticoids can be stopped without testing due to low concern for HPA axis suppression. (⊕○○○)

- While adrenal insufficiency is unlikely after **short-term** glucocorticoid therapy, **clinicians should be aware that even short-term glucocorticoid treatment** can **lead to complications such as increased incidence of sepsis, gastrointestinal bleeding, thromboembolism, and fractures.**

R 2.2—Glucocorticoid taper for patients on long-term glucocorticoid therapy should only be attempted if the underlying disease for which glucocorticoids were prescribed is controlled, and glucocorticoids are no longer required.

In these cases, glucocorticoids are tapered until approaching the physiologic daily dose equivalent is achieved (eg, 4-6 mg prednisone). (Good clinical practice)

- **Rationale**

- Glucocorticoids should only be **tapered if the underlying disease no longer requires glucocorticoid therapy.**
- In general, glucocorticoid taper **can be faster and in larger decrements if the total daily glucocorticoid dose is high (eg, greater than 30 mg of prednisone).**

- As the total daily glucocorticoid dose is **approaching the physiologic daily dose equivalent** (greater than equivalent of 15-25 mg hydrocortisone, 4-6 mg prednisone, see Table 1), **the taper should be slower and with smaller decrements** (Table 4).

- In certain patients with **glucocorticoid-induced complications**, such as uncontrolled **hypertension and hyperglycemia, glucocorticoid-induced psychosis, or herpetic keratitis,** a **more rapid** glucocorticoid **taper** towards physiologic daily dose equivalent may be required.

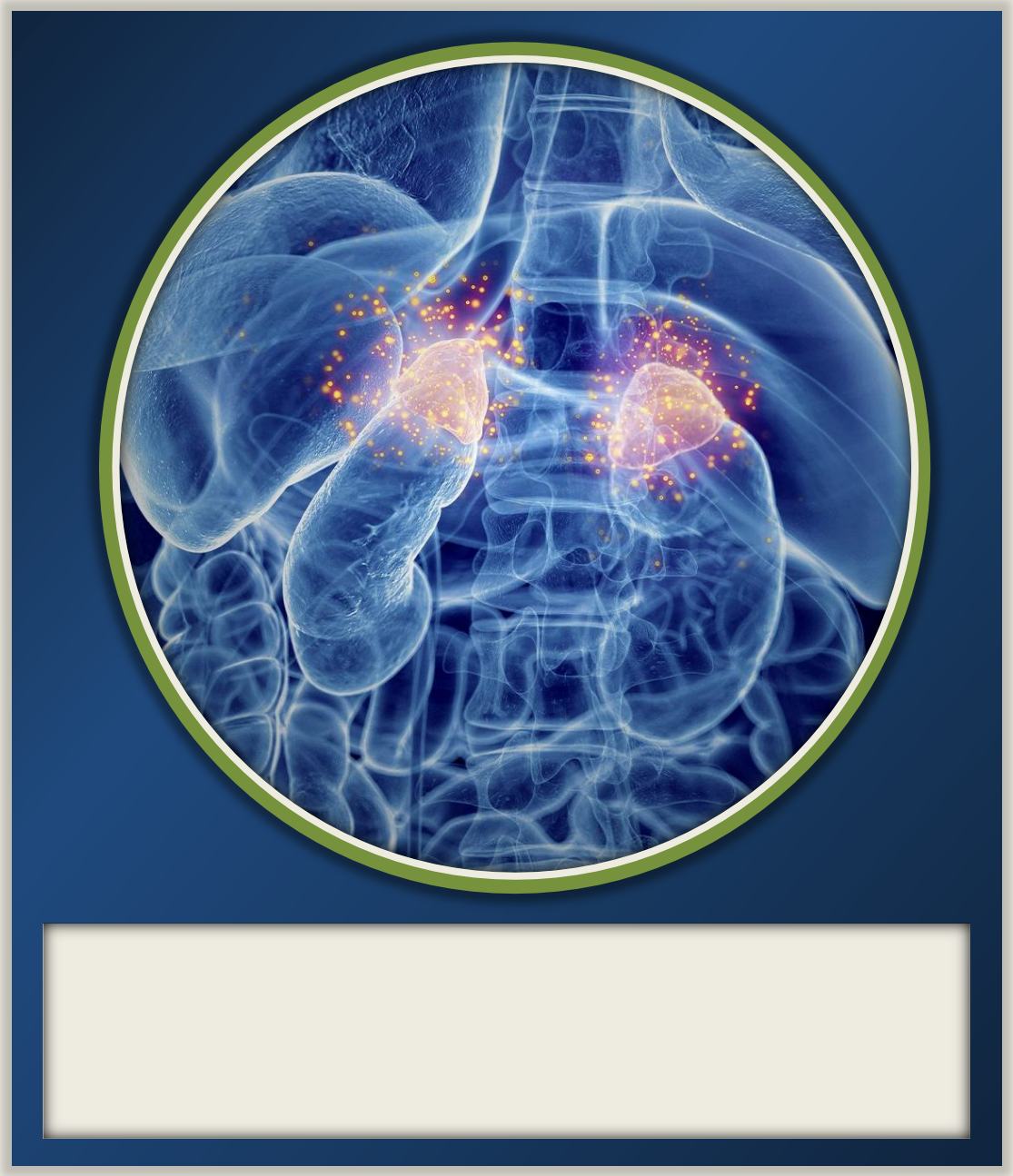
- The pre-test probability of **adrenal atrophy** and **concurrent adrenal insufficiency is high for patients taking long-term supraphysiologic** glucocorticoid doses; **adrenal function testing is unnecessary until a physiologic glucocorticoid dose is achieved.**

- **HPA recovery** is possible **once the glucocorticoid therapy has been tapered to a near-physiologic daily dose** (eg, 4-6 mg prednisone). At this time, **taper or assessment for HPA recovery could be performed unless glucocorticoids at this dose are required for control of the underlying condition** (for example transplant, or polymyalgia rheumatica).
- It is **helpful to consider** the **likelihood of adrenal insufficiency** and **the risk of underlying disease flare** before planning further tapering.
- It is also important to **consider the underlying comorbidities** and **evaluate concurrent drugs that could impact glucocorticoid metabolism and overall glucocorticoid exposure.**

- In general, **older individuals** have **reduced drug clearance**, despite a small sample size in these studies, data suggest a **considerable and multifactorial inter-individual variability** in **what would be considered a physiological glucocorticoid dose**.

R 2.3

- We recommend consideration of glucocorticoid withdrawal syndrome that may occur during glucocorticoid taper.
- When glucocorticoid withdrawal syndrome is severe, glucocorticoid dose can be temporarily increased to the most recent one that was tolerated, and the duration of glucocorticoid taper could be increased. (Good clinical practice)



- **Rationale**

- **Glucocorticoid withdrawal syndrome** occurs due to dependence on **supraphysiologic glucocorticoids while decreasing the dose of glucocorticoids .**

- Patients should be informed that glucocorticoid withdrawal symptoms are expected to **occur during the glucocorticoid dose reduction** and what the **differences are between glucocorticoid withdrawal syndrome, adrenal insufficiency, and underlying disease flare.**

- It should be emphasized that an **insufficient glucocorticoid supply** is **not expected** to occur **when the glucocorticoid dose is greater than the physiologic daily dose equivalent**. As exceptions, it should be noted that the **glucocorticoid requirement** may be **significantly higher in the case of critical illness or that glucocorticoid absorption is not guaranteed in gastroenteritis.**
- Managing glucocorticoid withdrawal syndrome and glucocorticoid taper in these patients may be especially **challenging.**
- **Patients should be educated** on symptoms of glucocorticoid withdrawal to **avoid anxiety related to unexpected symptoms or reactive, unnecessary, or excessive increase in glucocorticoids.**

- **Glucocorticoid withdrawal syndrome** is reported to occur in **40-67% of patients** tapering glucocorticoids **following curative adrenalectomy in adrenal Cushing syndrome .**
- **Duration** of exogenous glucocorticoid use, glucocorticoid **dose** and **type,** and **individual susceptibility** likely impact the **severity and duration of glucocorticoid withdrawal**, but systematic studies are lacking.
- In a recent study investigating **glucocorticoid withdrawal syndrome** in patients **following curative surgery for endogenous hypercortisolism**, symptoms of glucocorticoid withdrawal syndrome included **arthralgias, myalgias, weakness, fatigue, sleep disturbances, and mood changes in up to 50% of patients.**

- Symptoms are thought to occur due to an **abrupt decrease in glucocorticoid exposure leading** to an **increase in inflammatory cytokines .**
- **Symptoms** of glucocorticoid withdrawal syndrome **overlap with those seen in patients with untreated or not optimally treated adrenal insufficiency** (Table 5), and **most patients with glucocorticoid withdrawal syndrome do have concomitant adrenal insufficiency.**

- Since **symptoms of adrenal insufficiency and glucocorticoid withdrawal significantly overlap**, **good clinical guidance to differentiate between** those is to **consider the total daily dose of glucocorticoids with high doses making adrenal insufficiency less likely.**
- For example, **a patient treated for several months with prednisone 20-40 mg might experience glucocorticoid withdrawal symptoms**, but concerns for **spontaneous symptoms and signs of adrenal insufficiency are only a concern once the taper reaches 5-7.5 mg.**

- The overall duration, type, and daily dose of glucocorticoid used should be considered when designing a glucocorticoid taper. Patients treated with **higher glucocorticoid doses, long- acting glucocorticoids, and for a longer duration of time** are likely to have **more glucocorticoid withdrawal symptoms.**

- Patients with **features of exogenous Cushing syndrome** are **more likely to have a challenging glucocorticoid taper course because of glucocorticoid withdrawal syndrome** (Table 5).

Table 5. Clinical features of adrenal insufficiency, glucocorticoid withdrawal syndrome and common underlying conditions

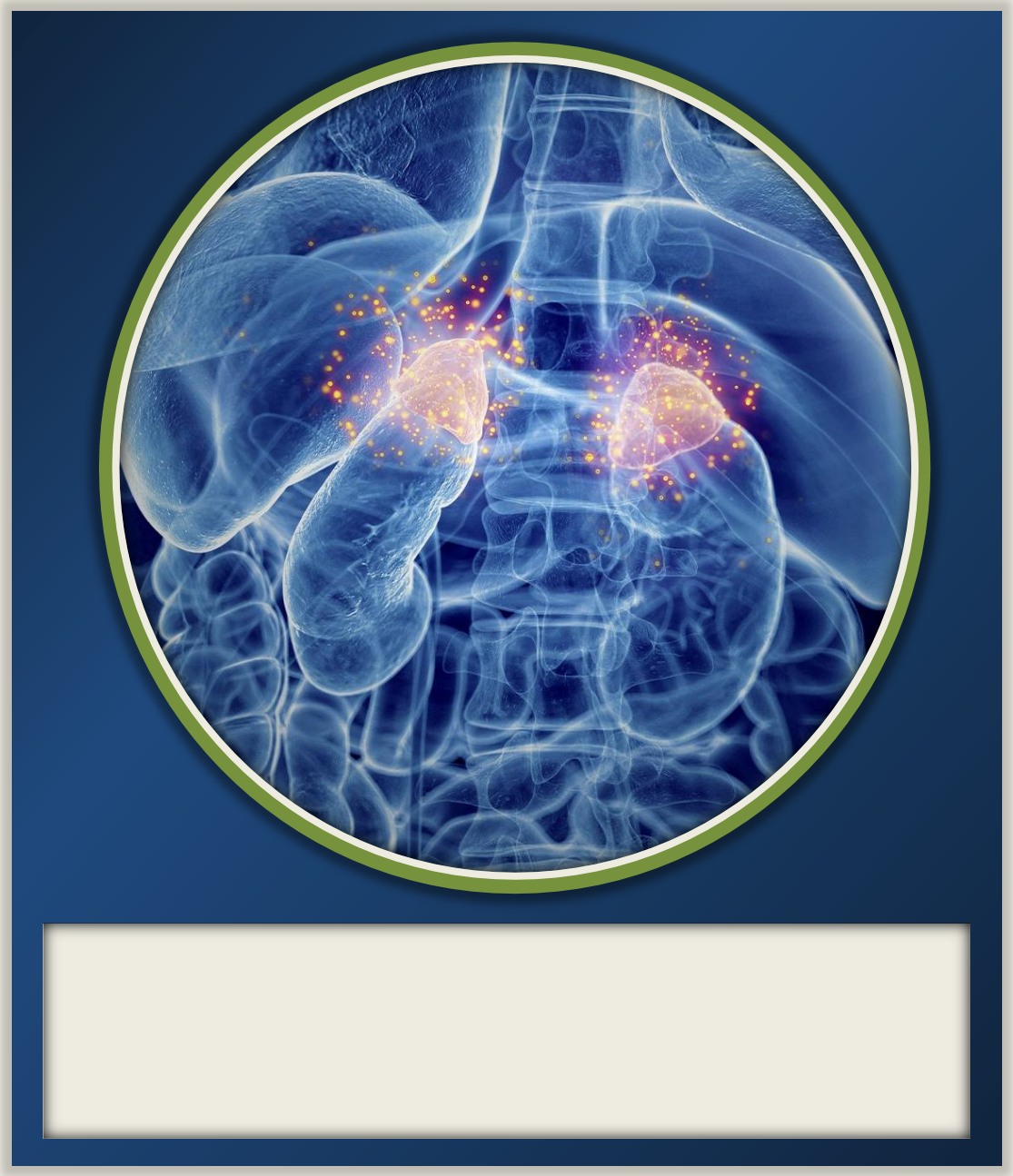
	Glucocorticoid withdrawal syndrome	Adrenal insufficiency	Underlying condition for which glucocorticoids were initially prescribed
Symptoms	General malaise, fatigue, nausea, muscle and joint pain, sleep disturbances, mood change	General malaise, fatigue, nausea, muscle and joint pain	Depending on condition (eg, joint pain in rheumatoid arthritis). Common overlapping symptoms (general malaise, fatigue)
Signs	Cushingoid features common, especially earlier in the glucocorticoid taper	Weight loss[a], hypotension, orthostasis	Disease-specific signs reappear
Timing of symptoms and signs occurrence	At any point during glucocorticoid taper, usually when prednisone is decreased <15 mg/day Higher risk with long-term supraphysiologic glucocorticoid therapy	Only when not treated with optimal glucocorticoid therapy (subphysiologic glucocorticoid dose, increased glucocorticoid requirements due to sickness)	At any point during glucocorticoid taper if the underlying condition is sub-optimally controlled with a non-glucocorticoid agent
Biochemistry	Normal electrolytes Glucocorticoid-induced hyperglycemia may be present	Hyponatremia, hypoglycemia	Biomarkers of disease activity (sedimentation rate, disease-specific biomarkers)
HPA axis	Testing is not recommended If tested, ACTH and cortisol are usually undetectable	Initially, low ACTH and cortisol Later in recovery: normal-elevated ACTH, low cortisol	Not applicable
Risk of adrenal crisis	Unlikely, if glucocorticoids are administered (as patients with glucocorticoid withdrawal syndrome also have adrenal insufficiency)	Yes, if not optimally treated with glucocorticoid therapy	Not applicable

- **Slow decrease in glucocorticoid dose** is the only known intervention that may help **prevent severe glucocorticoid withdrawal symptoms.**

- **Clinical severity was calculated based on the presence of physical features and comorbidities potentially related to glucocorticoid excess**, and may also be applied in patients treated with supraphysiologic glucocorticoids when deciding on the rapidity of glucocorticoid taper, with **slower taper in patients with high clinical severity score**, and a more **rapid taper in patients with lower clinical severity score.**
- In a patient with **severe glucocorticoid withdrawal syndrome** despite a **slower glucocorticoid taper**, **increasing the glucocorticoid dose temporarily to the most recent dose prior to onset of glucocorticoid withdrawal syndrome will usually alleviate the symptoms**.

R 2.4

- We recommend against routine testing for adrenal insufficiency in patients on supraphysiologic doses of glucocorticoids, or if they are still in need of glucocorticoid treatment for the underlying disease. (Good clinical practice)

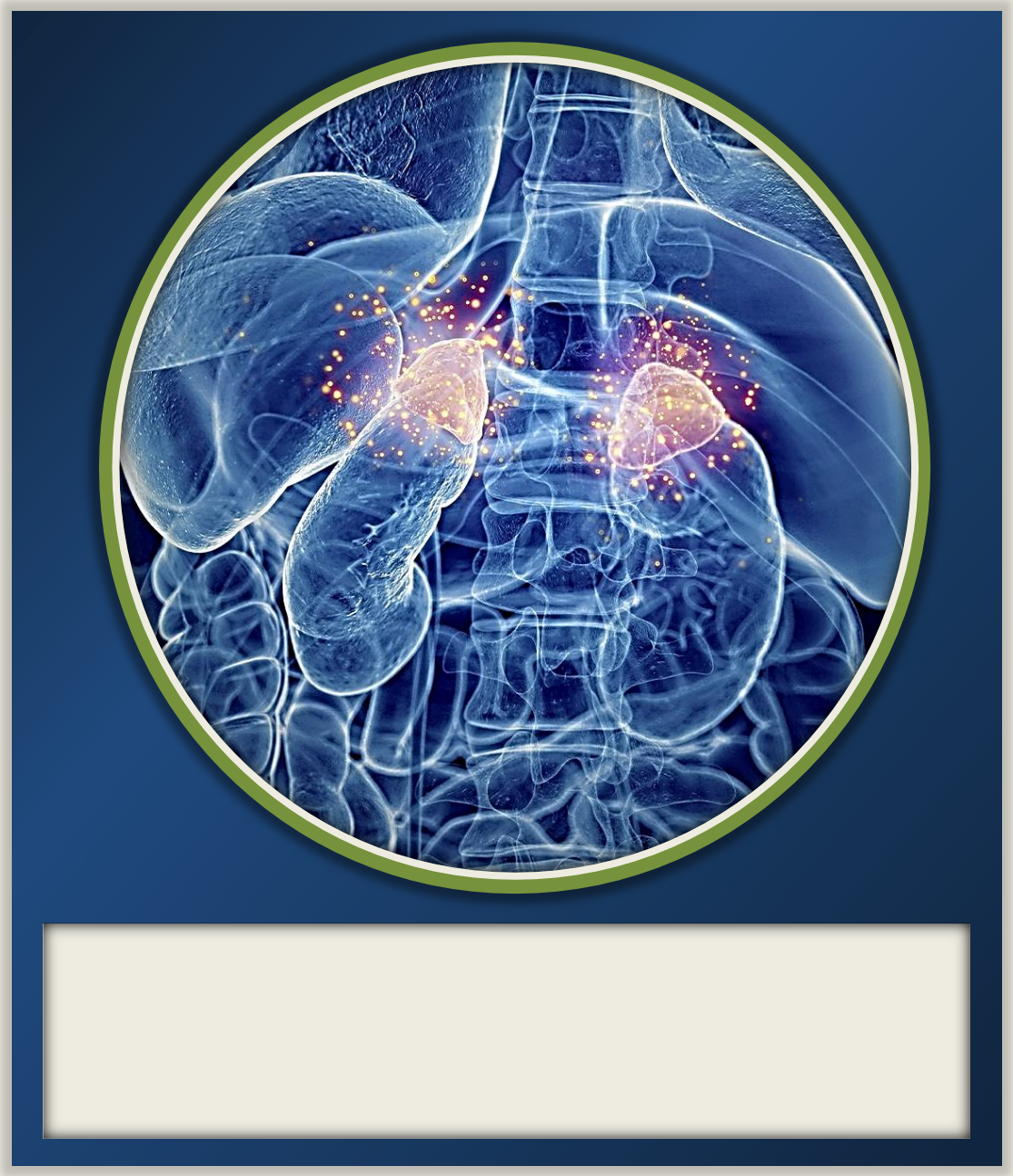


- **Rationale**

- If the glucocorticoid dose is in the **supraphysiologic** range, **suppression of the HPA axis** is expected and it is **unnecessary to test adrenal function.**
- Similarly, testing is **unnecessary in patients unable to stop glucocorticoid treatment**, for example patients with organ transplants and in cases of polymyalgia rheumatica.

R 2.5

- We suggest that patients taking long-acting glucocorticoids (eg, dexamethasone or betamethasone) should be switched to shorter-acting glucocorticoids (eg, hydrocortisone or prednisone) when long-acting glucocorticoids are no longer needed. (⊕○○○)



- **Rationale**

- The use of **long-acting glucocorticoids** with **higher glucocorticoid potency** predisposes to a **more pronounced suppression of HPA axis** and subsequent adrenocortical function impairment.

- **Long-acting glucocorticoids** such as **dexamethasone or betamethasone**, **even in physiologic daily dose** equivalent, are more likely to **cause HPA axis suppression, exogenous Cushing syndrome, and glucocorticoid withdrawal syndrome when being tapered .**

- **HPA axis recovery is impossible** in the setting of continuous **administration of long-acting glucocorticoids**.

- In contrast**, intermediate- or short-acting glucocorticoids**—which have both a **shorter biological half-life and lower glucocorticoid potency**—are more likely to allow **HPA recovery**,

- If **treatment with long-acting glucocorticoids is no longer needed,** we recommend **changing to shorter-acting formulations** such as **prednisone, prednisolone, hydrocortisone**, or **cortisone acetate** to promote recovery of the HPA axis.
- For patients on **non-oral glucocorticoids**, eg, **inhaled steroids**, in whom there is a **concern for glucocorticoid-induced adrenal insufficiency**, **a switch to short-acting oral glucocorticoids would be appropriate** when **non-oral glucocorticoids or no longer needed.**

- Moreover, **there is no compelling evidence** to **switch intermediate-acting glucocorticoids** such as **prednisone** to **hydrocortisone or cortisone acetate** to **further promote the recovery of the HPA axis.**

R 2.6—We suggest that patients on a physiologic daily dose equivalent, and aiming to discontinue glucocorticoid therapy, either:

1. continue to gradually taper the glucocorticoid dose, while being monitored clinically for signs and symptoms of adrenal insufficiency, or

2. be tested with a morning serum cortisol. (⊕○○○)

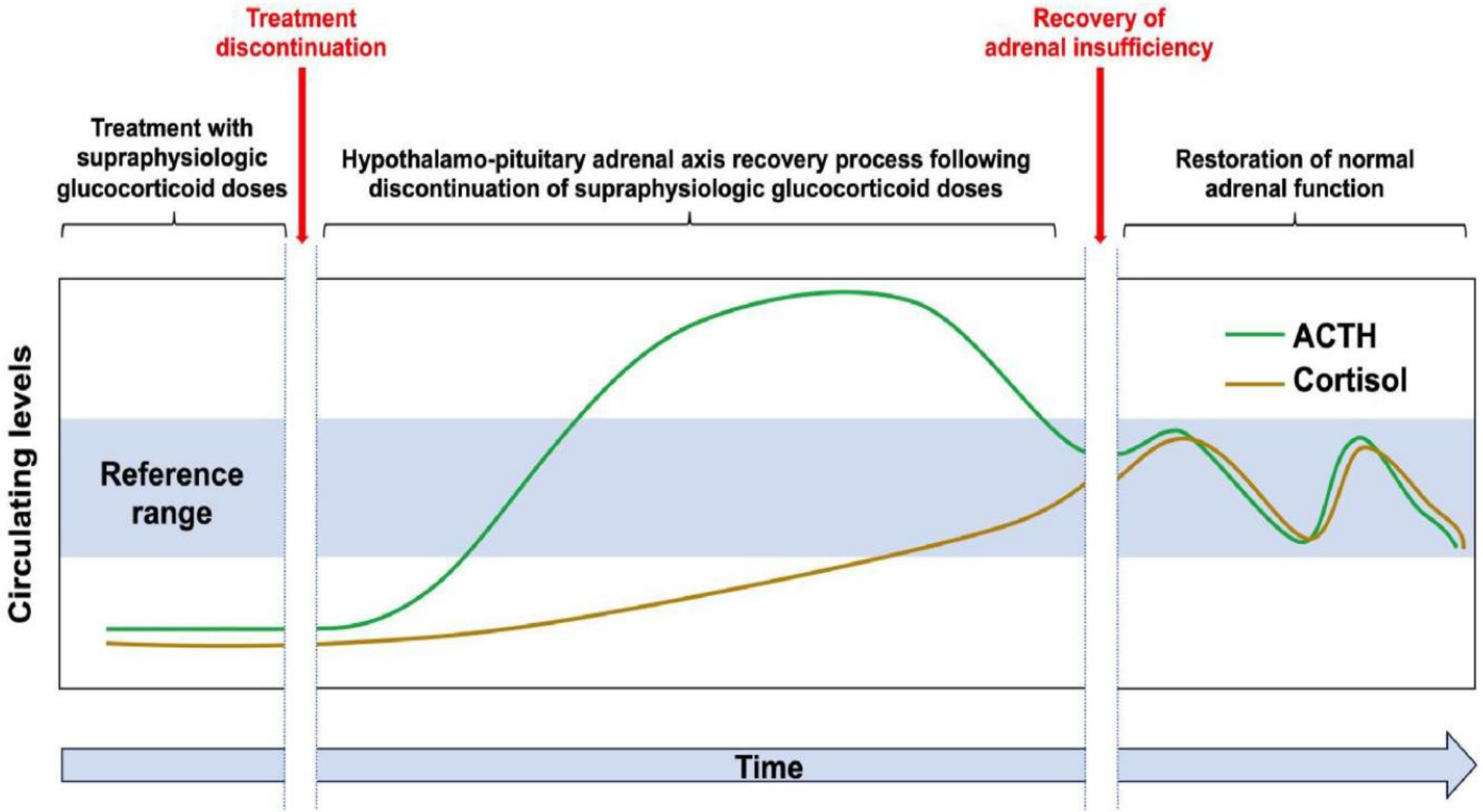


Figure 1. Schematic representation of HPA axis recovery following discontinuation of supraphysiologic glucocorticoid therapy (adapted from: Prete and Bancos 2021 (58)).

- While some authors recommend **a rapid reduction of the glucocorticoid dose to slightly above physiologic daily dose equivalent (eg, 7.5 mg prednisone),** followed by a **further reduction in smaller steps**,
- **others prefer testing of HPA axis to guide further tapering or immediate discontinuation**, if normal adrenocortical function is demonstrated.
- **Once glucocorticoids are tapered down to physiologic replacement doses**, the panel suggests **two possible approaches for the discontinuation of glucocorticoid therapy** (Fig. 2).

- Patients **may gradually taper glucocorticoids** while being **cautiously monitored for clinical manifestations of adrenal insufficiency.**

If the patient **experiences signs and symptoms of adrenal insufficiency**, **glucocorticoid regimen should be restarted and not discontinued until recovery of HPA axis is documented.**

If the patient **does not experience any symptoms**, the **tapering proceeds until glucocorticoid discontinuation**.

- Alternatively, **patients may undergo testing with a morning serum cortisol** (sample collected between 8:00 and 9:00 AM) for the determination of HPA axis recovery (R 2.7).

If adrenal insufficiency is documented, **exogenous glucocorticoid should not be reduced below the lower end of physiologic replacement dose ranges** to ensure adequate replacement for adrenal insufficiency, yet still providing a stimulus for HPA-axis recovery.

R 2.7—If confirmation of recovery of the HPA axis is desired, we recommend morning serum cortisol as the first test.

As a guide:

1.

- we suggest that the test indicates recovery of the HPA axis if **cortisol is >300 nmol/L or 10 µg/dL** and glucocorticoids can be **stopped** safely;

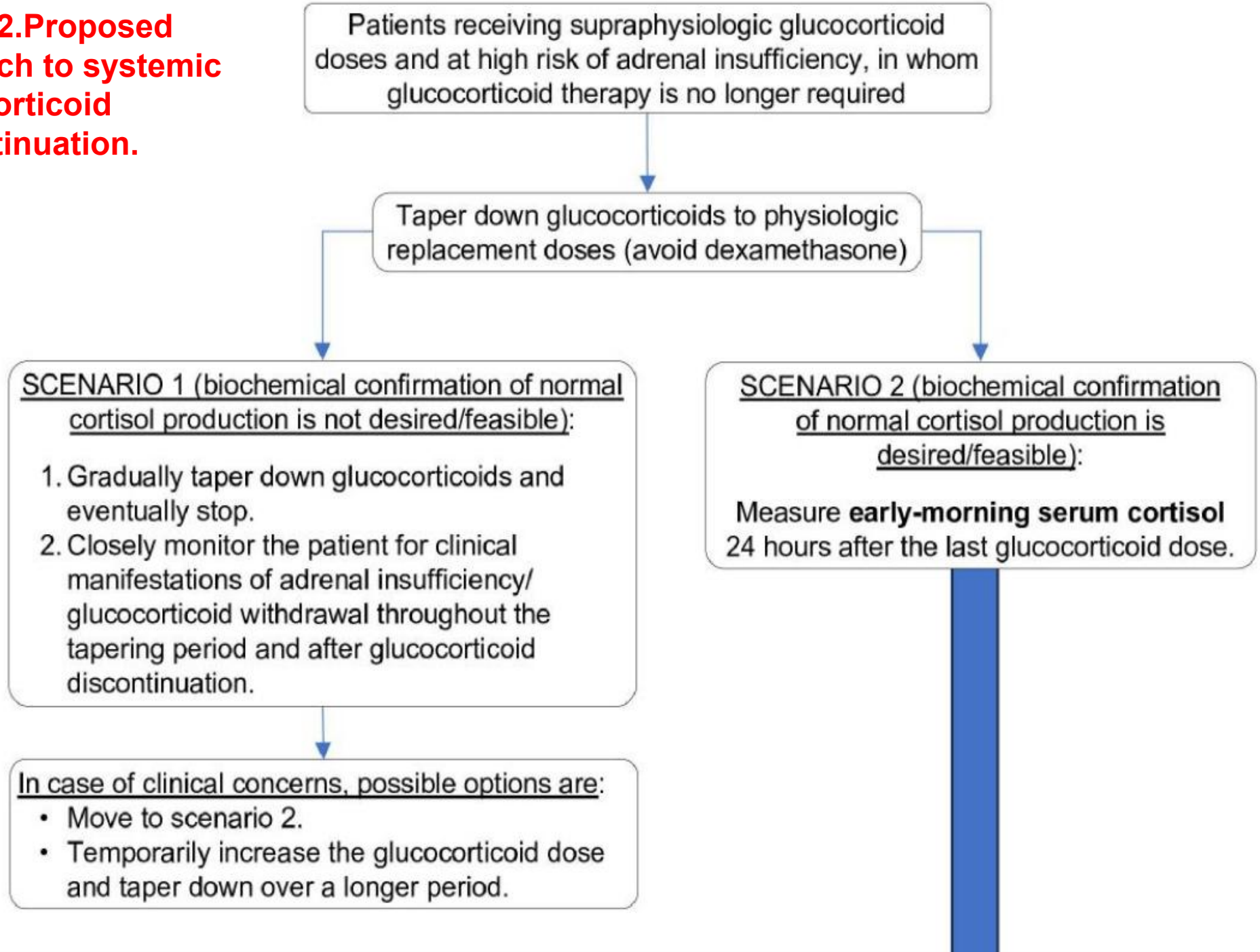
2.

- we suggest that if the result is between **150 nmol/L or 5 µg/dL and 300 nmol/L or 10 µg/dL,** the **physiologic glucocorticoid dose should be continued,** and the **morning cortisol repeated after an appropriate time period** (usually weeks to months);

3.

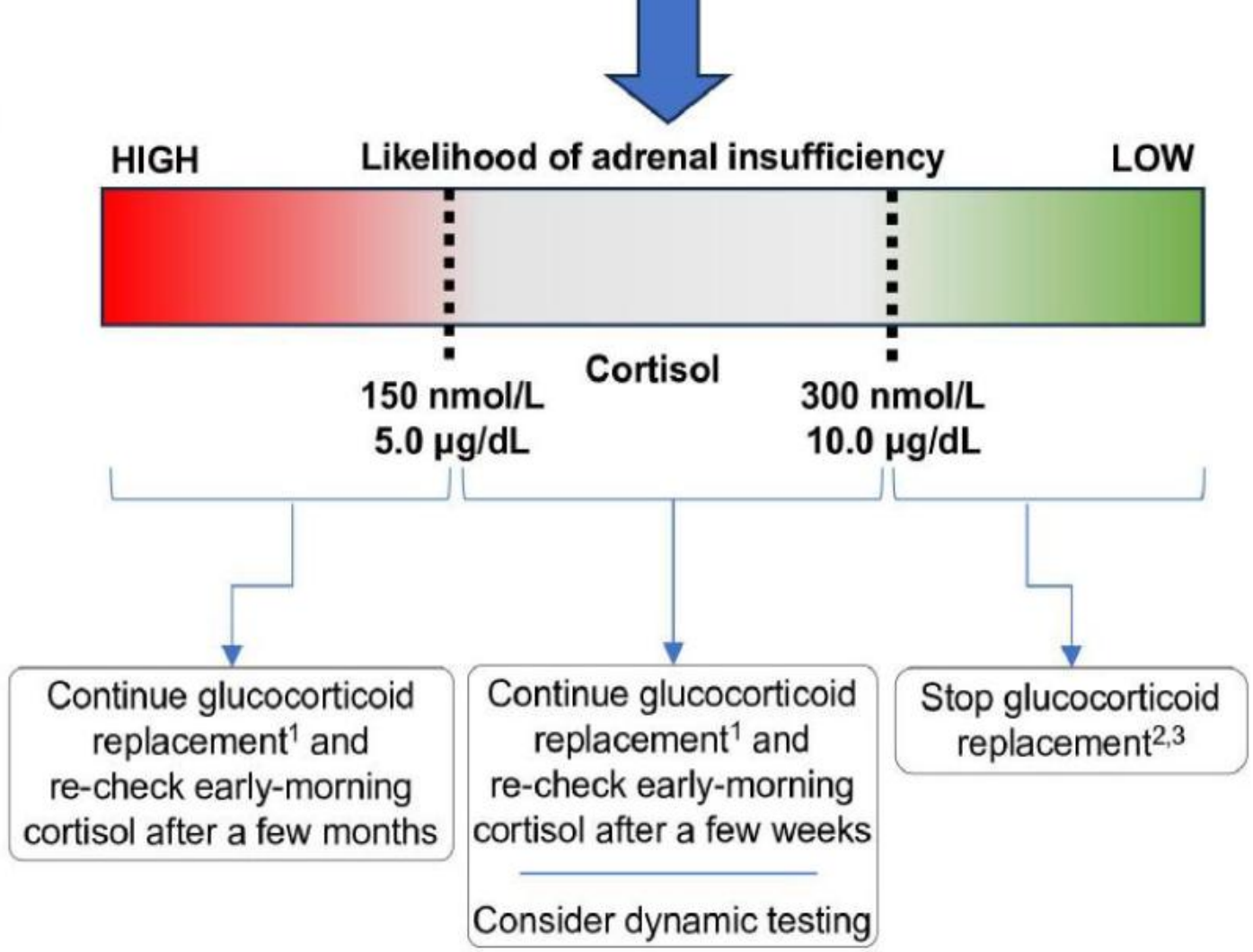
- we suggest that if the result is **<150 nmol/L or 5 µg/dL,** the **physiologic glucocorticoid dose should be continued**, and the morning cortisol **repeated after a few months.**

Figure 2.Proposed approach to systemic glucocorticoid discontinuation.



Important considerations:

- **The proposed cortisol cut-offs are only a guide and may vary according to the cortisol assay used and local protocols.**
- **The proposed cortisol cut-offs only apply to patients who are not under major stress (e.g., sepsis, trauma, surgery, or other acute illness requiring hospital admission).**
- **The proposed cortisol cut-offs do not apply to subjects with abnormal CBG and albumin (e.g., use of oral estrogens, pregnancy, advanced liver cirrhosis, nephrotic syndrome).**



Rationale

- Due to the ease/convenience of testing, experience and validation, a **morning serum cortisol level** (measured between 8:00 and 9:00 AM, **after holding glucocorticoid dose for at least 24 hours(excluding dexamethasone).**) is the recommended test to examine for **recovery of HPA axis** following glucocorticoid therapy (see also results of Clinical Question III).
- The test should be done only **after reaching the range of a physiologic equivalent daily dose** (eg, prednisone 4-6 mg daily or hydrocortisone 15-25 mg total daily dose, see Definitions).
- Patients with very low morning cortisol levels **(as a guide: <150 nmol/L (5 µg/dL))** are very likely to have **persistent adrenal insufficiency**. In such cases, dynamic testing is unlikely to be useful.

- In patients with higher serum cortisol levels but **below 300 nmol/L (10 µg/dL),** HPA axis **recovery is possible**.
- In such cases, we suggest that the most cost-effective and practical strategy is that these patients **continue with physiologic daily dose equivalent glucocorticoid replacement** and have morning serum cortisol re-checked **every few weeks until recovery occurs**.

- **If cortisol levels remain between 150 nmol/L (5 µg/dL) and 300 nmol/L (10 µg/dL), dynamic testing** can be considered.

Cortisol production is affected by the **sleep-awake cycle**, with cortisol secretion reaching its **peak just minutes before waking up.**

Thus, morning serum cortisol can appear **falsely low** in individuals with **disrupted circadian rhythm** (eg, **night shift workers, jet lag, and severe insomnia) .**

In addition, **serum cortisol concentrations** can be **elevated** in patients with **elevated cortisol-binding globulin**, such as seen during **pregnancy and in women on oral estrogens .**

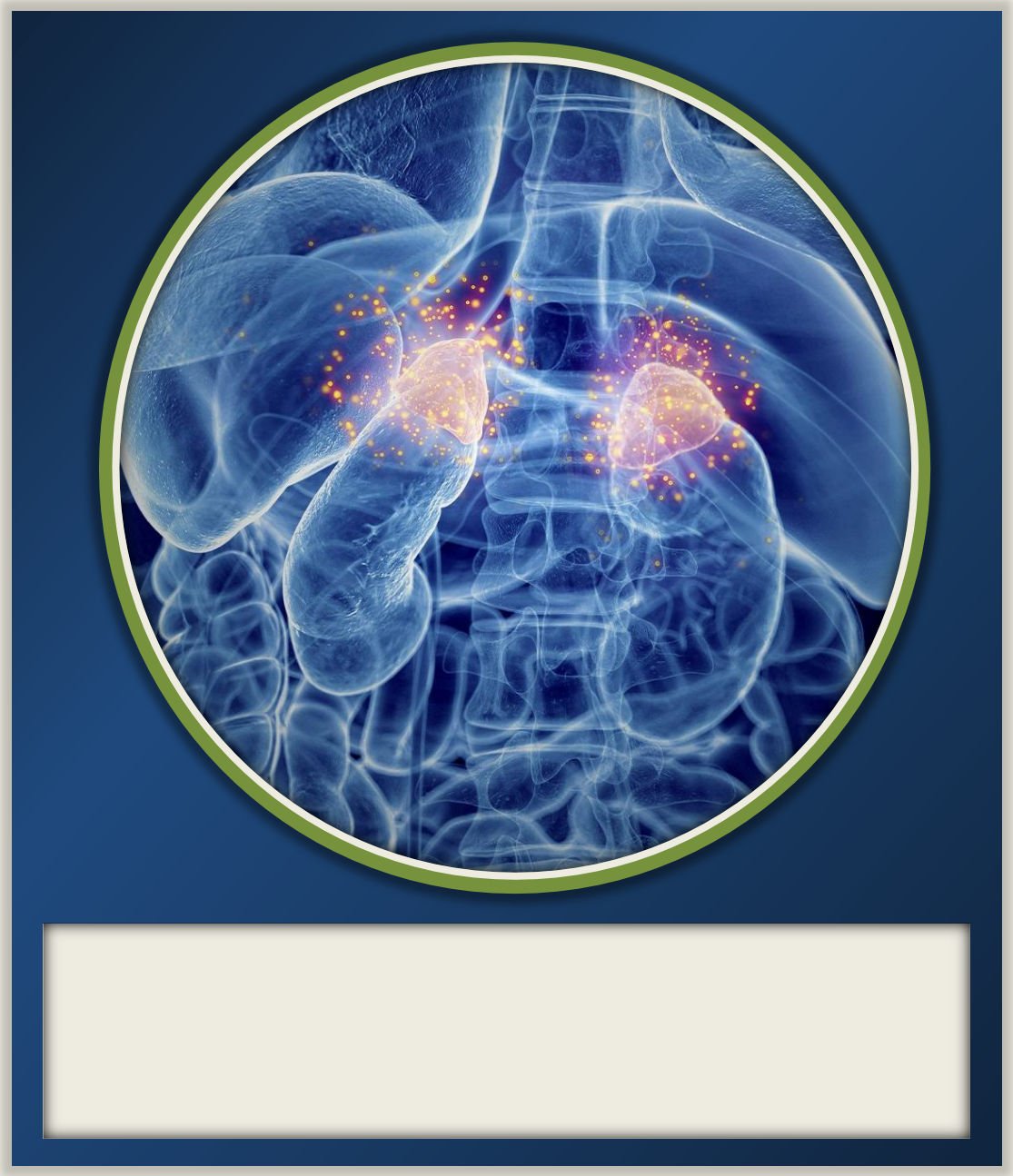
- By contrast, **serum cortisol concentrations** can be **decreased** in patients with **low albumin and cortisol binding globulin**, as in **hypoalbuminemic states** (such as advanced **cirrhosis, nephrotic syndrome, and malnutrition**), and **prolonged critical illness**.

- Concomitant measurement of **baseline DHEAS** was reported to have **a good diagnostic accuracy** in making a diagnosis of **secondary adrenal insufficiency,** including those with glucocorticoid-induced adrenal insufficiency.
- **Data on DHEAS use to diagnose recovery from glucocorticoid-induced adrenal insufficiency are scarce**, but suggest that normalization of **cortisol secretion occurs prior to normalization of DHEAS**, making it a less favorable laboratory value to detect adrenal axis recovery.

- promising alternative is **waking salivary cortisone** or **cortisol.**
- This **non-invasive and practical ambulatory** test holds the promise of **replacing in-hospital assessments** to test for adrenal insufficiency, but is currently **not widely available**.

R 2.8

- We suggest against routinely performing a dynamic test for diagnosing adrenal insufficiency in patients tapering or stopping glucocorticoid therapy. (⊕○○○)



- **Rationale**

- **Morning cortisol measurement** can serve as a simple approach to HPA axis assessment, obviating the need for other tests in many patients (see recommendation 2.7) .
- However, **if cortisol remains indeterminate** (see 2.7), **dynamic testing can be considered.**
- Dynamic testing options include **250 µg ACTH (1-24)** and, less commonly, **overnight metyrapone** and **insulin tolerance tests**.

R 2.9—We suggest awareness of possible glucocorticoid- induced adrenal insufficiency in patients:

1. with current or recent use of non-oral glucocorticoid formulations presenting with signs and symptoms indicative of adrenal insufficiency, or
2. using multiple glucocorticoid formulations simultaneously, or
3. using high dose inhaled or topical glucocorticoids, or
4. using inhaled or topical glucocorticoids for >1 year, or
5. who received intra-articular glucocorticoid injections in the previous 2 months, or
6. receiving concomitant treatment with strong cytochrome P450 3A4 inhibitors.

- We suggest that **glucocorticoid-induced adrenal insufficiency** should be suspected in patients with **current or recent use of non-oral glucocorticoid formulations presenting with signs and symptoms indicative of adrenal insufficiency** (Table 5).

- **Patients receiving multiple types of glucocorticoids** (eg, oral and inhaled) are **more susceptible to developing glucocorticoid-induced adrenal insufficiency**, reflecting the cumulative risk of systemic absorption and impact on the HPA axis.

- In patients treated with **inhaled glucocorticoids**, the risk correlates directly with treatment **dose and duration.**

- A total of **21.5%** (95%CI 12.0-35.5) of **patients using high doses of inhaled glucocorticoids** and **27.4%** (95%CI 17.7-39.8) of those **treated for more than 1 year** were found to have biochemical evidence of glucocorticoid-induced adrenal insufficiency (Table 6).

- Of note, **among all inhaled glucocorticoids fluticasone propionate** is most frequently associated with the development of **symptomatic glucocorticoid-induced adrenal insufficiency and exogenous Cushing syndrome.**
- Regarding **intranasal glucocorticoid** use, the risk of glucocorticoid-induced adrenal insufficiency is **low for short-term use** at the recommended doses (Table 6).
- However, several **intra-nasal glucocorticoids have high bioavailability and glucocorticoid receptor binding affinity**, which can result in **significant systemic exposure after prolonged use.**

- Robust **evidence about** the **impact of intra-articular glucocorticoid injections** on the HPA axis is **lacking**. Glucocorticoids can be detected in **the urine for months after injections** suggesting prolonged systemic absorption.
- We suggest that patients are **monitored for signs and symptoms of adrenal insufficiency** and that **healthcare professionals have** a low threshold for testing especially within **2 months of injections** and in patients who receive **simultaneous or multiple injections over a short period.**

- Commonly used **intra-articular** glucocorticoid preparations often lead to a **suppression of 4 weeks** and therefore **low morning cortisol values are expected during that time frame**, and recovery can be confirmed in the following 4 weeks.
- Evidence regarding **epidural glucocorticoid injections** is also **very limited** but patients receiving **multiple injections** and **higher doses** appear to carry a **higher risk of glucocorticoid-induced adrenal insufficiency.**

- **Most glucocorticoids are metabolized by the hepatic cytochrome P450 3A4 (CYP3A4).**
- Strong **CYP3A4 inhibitors**— which include **food ingredients** such as **grapefruit juice, several antibiotics, antifungals, and the protease inhibitor ritonavir** among others—have been shown to significantly **increase circulating concentrations** of glucocorticoids and hence substantially **increase the risk of suppressing HPA axis.**

Table 6. Non-oral glucocorticoid formulations and risk of glucocorticoid-induced adrenal insufficiency

	Prevalence of glucocorticoid-induced adrenal insufficiency[a]	Factors increasing the risk of glucocorticoid-induced adrenal insufficiency	Strategies to mitigate the risk of glucocorticoid-induced adrenal insufficiency[b]
Inhaled glucocorticoids	• Overall: 7.8% (CI 4.2-13.9) • Short-term use (<1 month): 1.4% (CI 0.3-7.4) • Medium-term use (1-12 months): 11.9% (CI 5.8-23.1) • Long-term use (>12 months): 27.4% (CI 17.7-39.8) • Low dose use: 2.4% (0.6-9.3) • Intermediate dose use: 8.5% (4.2-16.8) • High dose[c] use: 21.5% (12.0-35.5)	• Treatment with high doses[c] for prolonged periods • Use of fluticasone propionate • Concomitant use of other glucocorticoid formulations (eg, oral glucocorticoids in chronic obstructive pulmonary disease or nasal glucocorticoids for rhinitis/nasal polyposis) • Lower body mass index • Higher compliance with treatment • Concomitant treatment with strong cytochrome P450 3A4 inhibitors[d] (eg, medications containing ritonavir; antifungal drugs for acute allergic bronchopulmonary aspergillosis)	• Use the lowest effective glucocorticoid dose for the shortest period • Use spacers and mouth rinsing • Consider alternative glucocorticoids to fluticasone propionate • Avoid co-administration with strong cytochrome P450 3A4 inhibitors[d]
Intra-articular glucocorticoids	52.2% (40.5-63.6)	• Repeated injections over a short period (<3 months) • Simultaneous injections of multiple joints • Use of high glucocorticoid doses • Inflammatory arthropathies • Concomitant use of other glucocorticoid formulations • Concomitant treatment with strong cytochrome P450 3A4 inhibitors[d]	• Reduce the number of injections, if possible • Space out injections by at least 3-4 months, if possible • Triamcinolone hexacetonide may carry a lower risk of systemic absorption than triamcinolone acetonide • Avoid co-administration with strong cytochrome P450 3A4 inhibitors[d]

Percutaneous (topical) glucocorticoids	4.7% (CI 1.1-18.5)	• Long-term use of high-potency glucocorticoids on large surface areas or areas of increased absorption (eg, mucosa) • Prolonged use on inflamed skin with impaired barrier function • Occlusive dressings • Use on mucous membranes, eyelids, and scrotum • Concomitant use of other glucocorticoid formulations • Concomitant treatment with strong cytochrome P450 3A4 inhibitors[d]	• Use the smallest effective quantity for the shortest period • Use lower potency glucocorticoids, if possible • Avoid co-administration with strong cytochrome P450 3A4 inhibitors[d]
Intra-nasal glucocorticoids	4.2% (CI 0.5-28.9)	• Long-term use • Concomitant use of other glucocorticoid formulations • Concomitant treatment with strong cytochrome P450 3A4 inhibitors[d]	• Use the lowest effective glucocorticoid dose for the shortest period • Avoid co-administration with strong cytochrome P450 3A4 inhibitors[d]

These doses are expressed as total daily doses and should be seen as a guide only. Doses are based on information from manufactures" summaries of product characteristics, Global Initiative for Asthma (2023), and the British National Formulary.
Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus.
[a]Based on a systematic review and meta-analysis of studies assessing the prevalence of biochemical impairment of the HPA axis, regardless of clinical correlates (24). Systematic data on the prevalence of signs and symptoms of adrenal insufficiency are lacking.
[b]Suggested strategies include consideration of reduced doses, frequencies, and alternative treatments, but sufficient control of the underlying glucocorticoid dependent disease remains paramount.
[c]High doses of commonly prescribed inhaled glucocorticoids in adults are:

- Fluticasone propionate >500 μg/day
- Beclometasone dipropionate (standard particle inhalers) > 1000 μg/day
- Beclometasone dipropionate (extra fine particle inhalers) > 400 μg/day
- Budesonide >800 μg/day
- Ciclesonide >320 μg/day
- Fluticasone furoate >200 μg/day
- Mometasone furoate standard particle >400 μg/day

R 2.10—We suggest that patients with current or previous glucocorticoid treatment presenting with signs and symptoms of exogenous Cushing syndrome are assumed to have glucocorticoid-induced adrenal insufficiency. (Good clinical practice)

- **Rationale**

- **Patients with a history of glucocorticoid treatment/exposure presenting with manifestations of Cushing syndrome** (Table 7) should be assumed to have a **fully suppressed HPA axis and managed accordingly.**

- Exogenous Cushing syndrome **can occur with any glucocorticoid formulation** and can **take several months to resolve** after the glucocorticoid daily dose is decreased to physiological range.

Table 7. Signs and symptoms of glucocorticoid-induced (exogenous) cushing syndrome

Symptoms	Muscle weakness
	Sleep disturbances (insomnia)
	Increased appetite
	Mood and cognitive disturbances (irritability, impaired memory, depression)
Signs	Proximal muscle weakness and wasting
	Excess weight gain and central obesity
	Supraclavicular and dorsocervical fat accumulation
	Facial and upper neck plethora with facial rounding
	Skin atrophy with easy bruising, red stretchmarks, and poor wound healing
	Acne
	Menstrual irregularities in women
Other manifestations	Cardiometabolic risk factors (hypertension, dysglycemia, dyslipidemia, hypercoagulability)
	Osteoporosis and fragility fractures
	Hypogonadism, reduced libido, and reduced fertility

R 2.11—We suggest that patients aiming to discontinue glucocorticoids, but without recovery of HPA axis in one year while on physiologic daily dose equivalent, should be evaluated by an endocrinology specialist.

We suggest that patients on glucocorticoids and history of adrenal crisis should also be evaluated by an endocrinology specialist. (Good clinical practice)

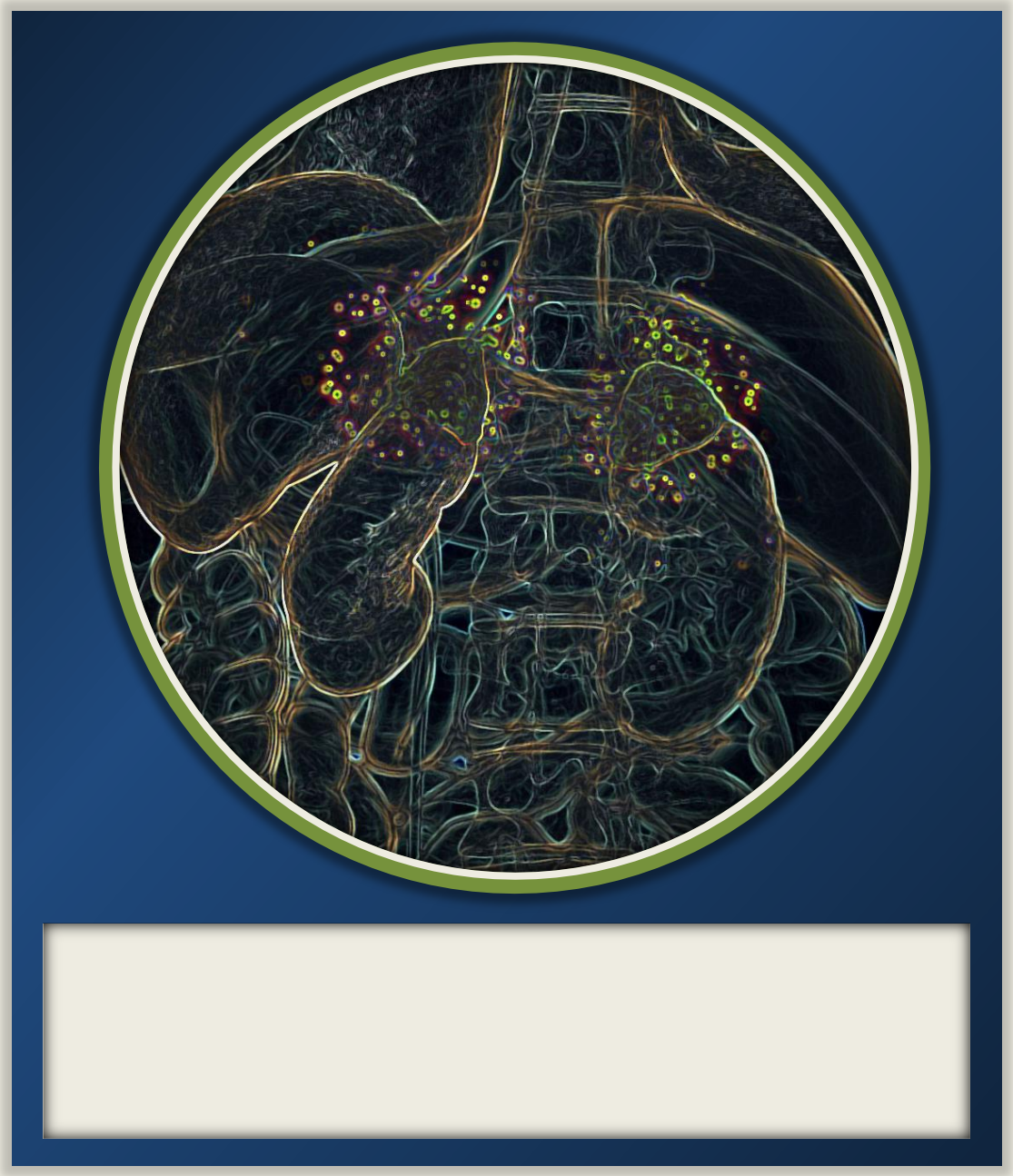
Rationale

- Prior studies have shown that **adrenal insufficiency may last** even up to **2-4 years after glucocorticoid cessation,** owing to slow recovery of adrenal cortisol production.

- **Persistent impairment of cortisol secretion beyond four years** suggests that **recovery of adrenal function is very unlikely** and **long-term glucocorticoid replacement should be continued**.
- The panel suggests that **patients with persistent adrenal insufficiency while on physiologic daily dose equivalent of glucocorticoids for longer than one year** should be evaluated by an endocrinology specialist to assess for **underlying causes of adrenal insufficiency other than glucocorticoid-induced adrenal insufficiency (eg, pituitary causes).**

R 2.12

- We recommend against the use of fludrocortisone in patients with glucocorticoid-induced adrenal insufficiency.



- **Rationale**

- Secretion of the mineralocorticoid aldosterone is largely regulated by the renin-angiotensin system and potassium levels.

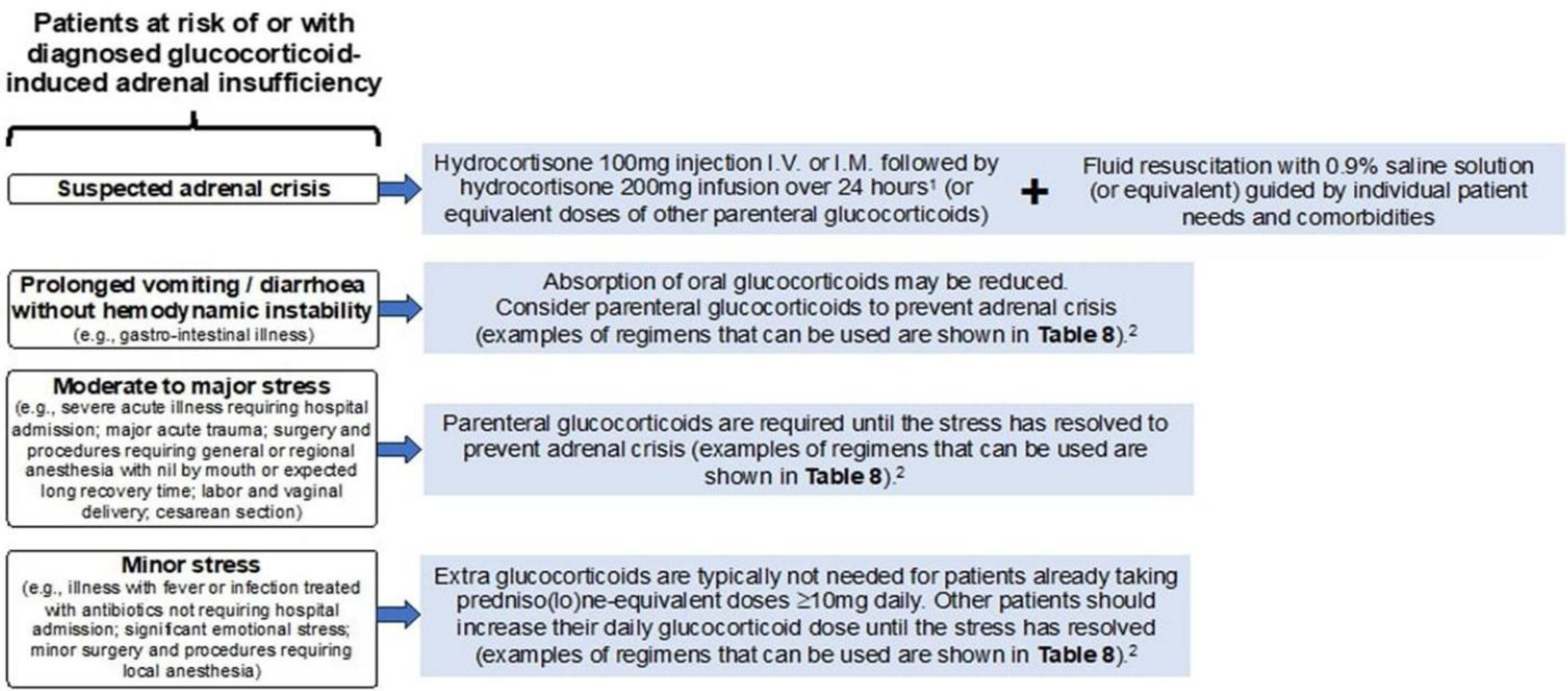
- Accordingly, mineralocorticoid function is expected to be **preserved in glucocorticoid-induced adrenal insufficiency**, as in other forms of secondary or tertiary adrenal insufficiency.
- **Substitution therapy with fludrocortisone is not indicated.**

3. Recommendations on diagnosis and therapy of adrenal crisis in patients with glucocorticoid-induced adrenal insufficiency.

R 3.1—We recommend that patients **with current or recent glucocorticoid use who did not undergo biochemical testing to rule out glucocorticoid-induced adrenal insufficiency** should **receive stress dose coverage when they are exposed to stress.** (Good clinical practice)

- **R3.1A—Oral glucocorticoids should be used in case of minor stress** and when there are **no signs of hemodynamic instability or prolonged vomiting or diarrhea.**

- **R3.1B—Parenteral glucocorticoids** should be used **in case of moderate to major stress, procedures under general or regional anesthesia, procedures requiring prolonged avoidance or inability of oral intake, or when there are signs of hemodynamic instability or prolonged vomiting or diarrhea.**



[1] Continue hydrocortisone infusion (or parenteral administration of other glucocorticoids) only in patients with confirmed adrenal crisis.

[2] The need for extra glucocorticoid cover and the regimen used must be guided by individual patient requirements and clinical judgment.

Figure 3. Management of patients at risk of or with diagnosed glucocorticoid-induced adrenal insufficiency with suspected adrenal crisis or during exposure to stress.

Table 8. Suggested glucocorticoid regimens in patients at risk of or with diagnosed glucocorticoid-induced adrenal insufficiency during exposure to stress

	General considerations	Examples	Suggested regimen
Minor stress	If the patient is already taking hydrocortisone ≥40 mg daily prednisone ≥10 mg daily, or dexamethasone ≥1 mg daily, there is typically no need to increase the dose unless there are signs of hemodynamic instability	• Illness requiring bed rest • Illness with fever (out of hospital) • Illness requiring treatment with antibiotics (out of hospital) • Significant emotional stress (eg, bereavement)	If not on daily glucocorticoids: give hydrocortisone 40 mg total daily dose, to be given in three divided doses (eg, 20 mg on rising, 10 mg 12 midday, 10 mg 5pm). Continue for 2-5 days until well (or for the duration of antibiotic treatment). If on hydrocortisone <40 mg total daily dose: increase to 40 mg total daily dose, to be given in three divided doses (eg, 20 mg on rising, 10 mg 12 midday, 10 mg 5pm). Continue for 2-5 days until well (or for the duration of antibiotic treatment). If on prednisone <10 mg total daily dose: increase to 10 mg total daily dose, to be given in one or two divided doses. Continue for 2-5 days until well (or for the duration of antibiotic treatment). If on dexamethasone <1 mg total daily dose: increase to 1 mg once daily. Continue for 2-5 days until well.

Minor surgery including any procedure requiring local anesthesia	If not on daily glucocorticoids: give oral hydrocortisone 40 mg total daily dose, to be given in three divided doses (eg, 20 mg one hour prior to the procedure, 10 mg six hours after the procedure, 10 mg after a further six hours). Continue glucocorticoids in patients who remain unwell after the procedure until clinically stable. If on hydrocortisone <40 mg total daily dose: increase to 40 mg total daily dose, to be given in three divided doses (eg, 20 mg one hour prior to the procedure, 10 mg six hours after the procedure, 10 mg after a further six hours). Continue increased dose in patients who remain unwell after the procedure until clinically stable. If on prednisone <10 mg total daily dose: increase to 10 mg total daily dose, to be given one hour prior to the procedure. Continue increased dose in patients who remain unwell after the procedure until clinically stable. If on dexamethasone <1 mg total daily dose: increase to 1 mg total daily dose, to be given one hour prior to the procedure. Continue increased dose in patients who remain unwell after the procedure until clinically stable.
Bowel procedures not carried out under general anesthesia	If not on daily glucocorticoids: give hydrocortisone 20 mg total daily dose, to be given in three divided doses (eg, 10 mg one hour prior to the procedure, 5 mg six hours after the procedure, 5 mg after a further six hours). If on daily glucocorticoids: continue normal glucocorticoid dose. Give an equivalent I.V. dose if prolonged nil by mouth.

Moderate and major stress	If the patient is already taking hydrocortisone ≥200 mg daily, prednisone ≥50 mg daily, or dexamethasone ≥6-8 mg daily, there is typically no need to increase the dose In patients with suspected reduced absorption (persistent vomiting or diarrhea), nil by mouth, or unable to take tablets, give stress-dose glucocorticoids I.V. or I.M. High body weight can be taken into	Severe intercurrent illness, for example: • Persistent vomiting or diarrhea from gastro-intestinal illness. • Infection requiring hospital admission or I.V. antibiotics (eg, sepsis). • Acute trauma resulting in significant blood loss or hospital admission.	For patients with persistent vomiting or diarrhea who are well enough to remain out of hospital: Hydrocortisone 100 mg I.M. injection immediately, which can be repeated after 6 hours if needed. If symptoms do not resolve or hemodynamic instability develops, admit to hospital for I.V. urgent glucocorticoid and fluid administration.

Table 8. Continued

General considerations	Examples	Suggested regimen
consideration as a factor indicating higher dosage requirements		Patients requiring hospital admission: Hydrocortisone 100 mg I.V. bolus or I.M. injection immediately, followed by immediate initiation of a continuous infusion of hydrocortisone 200 mg over 24 hours. If a continuous infusion is not feasible, give hydrocortisone 50 mg I.V. boluses every 6 hours. The duration and dose of the glucocorticoid regimen thereafter must be individualized based on the stressor type and the patient's clinical status.
	Surgery or any procedure requiring general or regional anesthesia with anticipated short recovery time and no nil by mouth	Intra-operative regimen: Hydrocortisone 100 mg I.V. bolus at induction, followed by immediate initiation of a continuous infusion of hydrocortisone 200 mg over 24 hours. If a continuous infusion is not feasible, give hydrocortisone 50 mg I.V. boluses every 6 hours. Postoperative regimen: Resume oral glucocorticoids at an increased dose for 48 hours (eg, hydrocortisone 40 mg/daily in three divided doses; prednisone 10 mg/daily in one or two divided doses; dexamethasone 1 mg once daily) and then resume the pre-surgical dose. In case of post-operative complications (eg, significant pain, infections), maintain an increased oral dose or give stress-dose glucocorticoids I.V. as clinically appropriate.

	Postoperative regimen: Continuous infusion of hydrocortisone 200 mg over 24 hours while the patient is nil by mouth. If a continuous infusion is not feasible, give hydrocortisone 50 mg I.V. boluses every 6 hours. If the post-operative period is uncomplicated and once the patient can eat, resume oral glucocorticoids at an increased dose for 48 hours (eg, hydrocortisone 40 mg/daily in three divided doses; prednisone 10 mg/daily in one or two divided doses; dexamethasone 1 mg once daily) and then resume the pre-surgical dose. In case of post-operative complications (eg, significant pain, infections), maintain an increased oral dose or give stress-dose glucocorticoids I.V. as clinically appropriate.
Labor and vaginal delivery	Hydrocortisone 100 mg I.V. bolus at onset of labor, followed by immediate initiation of a continuous infusion of hydrocortisone 200 mg over 24 hours. If a continuous infusion is not feasible, give hydrocortisone 50 mg I.V. boluses every 6 hours.

Table 9. Signs and symptoms of adrenal crisis and potential precipitating factors

General considerations	• Patients present with a shock out of proportion to the severity of the trigger, if a trigger is identified (see below) • The shock is typically resistant to inotropes and fluid resuscitation if the adrenal crisis is not recognized and promptly treated with parenteral glucocorticoids • Risk factors for adrenal crises include a history of previous adrenal crises, older age (>65 years), adolescence and transition from pediatric to adult care, and a higher comorbidity burden • Glucocorticoid tapering down and discontinuation are crucial times, as glucocorticoid-induced adrenal insufficiency can become clinically apparent
Diagnosis	Hypotension or hypovolemic shock plus at least one of the following: • Nausea or vomiting • Severe fatigue • Fever • Impaired consciousness (incl. lethargy, confusion, somnolence, collapse, delirium, coma, and seizures)
Possible laboratory abnormalities (not required for the diagnosis)	• Hyponatremia (typically with raised urinary sodium) • Hyperkalemia • Signs of volume depletion (eg, raised urea and creatinine) • Hypoglycemia • Lymphocytosis • Eosinophilia

Factors that can trigger an adrenal crisis or elicit symptoms of adrenal insufficiency

Common to all patients with adrenal insufficiency:

- Infections (including gastrointestinal, genitourinary, respiratory, and sepsis)
- Acute illness (including fever)
- Physical trauma
- Surgery or other procedures requiring general, regional, or local anesthesia
- Bowel procedures requiring laxatives/enema
- Labor and delivery
- Dental procedures
- Severe stress and pain (including severe anxiety and bereavement)
- Strenuous exercise

Specific to patients with glucocorticoid-induced adrenal insufficiency:

- Abrupt glucocorticoid withdrawal in subjects on long-term treatment
- Glucocorticoid tapering below physiological replacement doses
- Switch between different types, formulations, and doses of inhaled glucocorticoids, which can lead to considerable variability of glucocorticoid systemic absorption
- Initiation of strong cytochrome P450 3A4 inducers, which leads to increased liver metabolism of several glucocorticoids. Strong inducers include apalutamide, carbamazepine, enzalutamide, fosphenytoin, lumacaftor, lumacaftor-ivacaftor, mitotane, phenobarbital, phenytoin, primidone, and rifampicin

- Therefore, patients with **current or recent glucocorticoid use who did not undergo biochemical testing to rule out glucocorticoid-induced adrenal insufficiency** who are **under minor stress (eg, fever, infection requiring antibiotics, physical trauma, significant emotional stress) not leading to hemodynamic instability and with no evidence of oral glucocorticoid malabsorption (vomiting, diarrhea) or are undergoing a surgical procedure under local anesthesia** will require **coverage with stress dose of oral glucocorticoids** (as a general guide, see Table 8).
- The recommended **stress dose of hydrocortisone** is the same as for patients with primary or secondary adrenal insufficiency of other etiology: patients should receive double the physiologic replacement dose (ie, **hydrocortisone 40 mg daily**, usually split in **three doses 20 mg on rising, 10 mg 12midday, 10 mg 5PM)**

- **In patients using other glucocorticoid formulations**, a dose equivalent to **40 mg hydrocortisone** is suggested and this regime needs to be offered for the duration of the stress period eg, **prednisone 10 mg total daily dose** to be given in one or two divided doses (as a general guide, see Table 8).

- Particularly **for patients undergoing surgery under general or regional anesthesia associated with long recovery time**, **parenteral stress doses of hydrocortisone or equivalent doses** of other glucocorticoids such as methylprednisolone or dexamethasone are recommended (as a general guide, see Table 8).

R 3.2—We suggest that in patients with current or recent glucocorticoid use who did not undergo biochemical testing to rule out glucocorticoid-induced adrenal insufficiency and present with hemodynamic instability, vomiting, or diarrhea, the diagnosis of adrenal crisis should be considered irrespective of the glucocorticoid type, mode of administration, and dose; patients with suspected adrenal crisis should be treated with parenteral glucocorticoids and fluid resuscitation. (Good clinical practice)

- **Rationale**

- **Adrenal crisis** (also known as acute adrenal insufficiency or Addisonian crisis) can **occur in patients taking oral supraphysiologic doses of glucocorticoids, if drug availability suddenly decreases** (eg, missed doses, gastroenteritis).

- It is a **life-threatening emergency** that must be promptly recognized and treated.

- **Treatment must not be delayed** by laboratory or imaging investigations. If an established or impending adrenal crisis is suspected, the patient should **immediately receive an injection of 100 mg hydrocortisone intravenously or intramuscularly** followed by rapid **volume resuscitation** withintravenous administration of 0.9% saline solution (or equivalent) .

- Patients with confirmed adrenal crisis should be maintained on **hydrocortisone at a dose of 200 mg hydrocortisone per 24 hours (preferably by continuous intravenous infusion, alternatively by intravenous or intramuscular injection of 50 mg hydrocortisone every 6 hours)** until clinical recovery and further guidance by an endocrinology specialist

- In patients with **very high body weight, higher doses might be considered.** Some centers use **equivalent parenteral doses** of other glucocorticoids such as **methylprednisolone or dexamethasone;** head-to-head comparison data of different treatment strategies for adrenal crisis are lacking.

- **Adrenal crisis prevention** is **one of the main goals of the management of any patient with adrenal insufficiency** and is achieved through **regular patient education** about its **signs and symptoms, possible precipitating factors** (see recommendations 1.2 and 1.3, Table 9), **when and how to increase glucocorticoid dose (sick day rules)**, and the **provision of patient-held prompts to healthcare professionals** should they become seriously ill or unconscious.

- These observations **highlight** **the need for prevention strategies and education of patients and healthcare professionals alike**.

Future Research

- **Evidence** for the majority of above recommendations regarding **glucocorticoid-induced adrenal insufficiency** is **low or very low.** Therefore, future epidemiology research needs to define the **true risk of clinical adrenal crisis and adrenal insufficiency.**

- There is a **need for further definition of risk factors contributing to the development and susceptibility of adrenal insufficiency**, such as **genetic predisposition, environmental influences, concurrent medication and underlying disease** for which glucocorticoid therapy is initiated for.

- **More specific and predictive tests and follow-up parameters** (including **salivary cortisol and potentially continuous monitoring of interstitial cortisol) are needed to identify at-risk patients** who would benefit from dedicated preventive intervention.

- **More research is needed aiming to identify glucocorticoids retaining immunosuppressive and anti-inflammatory properties, but having less effect on HPA axis suppression** and an **improved adverse effect profile**.

- In addition, **the exploration of other therapeutic strategies,** such as **concurrent HPA axis stimulation to prevent suppression** should also be entertained.

- There is a need for **a harmonization of cortisol assays**. While most cut-off values were established using **different immunoassays**, usually **overestimating true cortisol** values due to varying **degrees of cross-reactivity with other steroid metabolites,** the advent of **mass spectrometry** allows for a specific measurement of cortisol.

IMPORTANT MEDICAL INFO

THIS PATIENT NEEDS DAILY REPLACEMENT THERAPY WITH CORTISONE

In case of serious illness, trauma, vomiting or diarrhoea; hydrocortisone 100mg iv/im and iv saline infusion should be administered **WITHOUT DELAY**.

_____

Name

_____

Date of birth

European Society of Endocrinology


Thank you !
For your attention