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EASILY MISSED?

# Glucocorticoid induced adrenal insufficiency

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**What you need to know**

- Educate patients taking prednisolone ≥5 mg/day or equivalent for more than four weeks, 40 mg prednisolone or equivalent for longer than one week, or repeated short courses of glucocorticoids via any route (≥3 per year), about the risk of glucocorticoid induced adrenal insufficiency (GC-AI)
- Advise patients at risk of GC-AI to increase their dose of glucocorticoid when unwell and issue them with a steroid emergency card

*A 72 year old woman presents to her general practitioner with a two week history of fatigue, nausea, and poor balance. She has recently completed a three month course of prednisolone for polymyalgia rheumatica. Investigations show she is euvolaemic with a serum sodium of 126 mmol/L (reference range 133-145 mmol/L), urine sodium 35 mmol/L, and urine osmolality 560 mOsm/kg. A serum cortisol is not measured. Based on her history and these results, she receives a diagnosis of syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and is advised to restrict her fluid intake. She reduces fluids, but experiences similar symptoms and worsening hyponatraemia in the subsequent four weeks, and is referred to hospital. On admission to hospital, her serum cortisol is 124 nmol/L (4.5 µg/dL), synacthen test shows suboptimal cortisol response (30 minute cortisol 216 nmol/L (7.8 µg/dL)), and adrenocorticotropic hormone (ACTH) is normal (7.4 ng/L). A diagnosis of glucocorticoid induced adrenal insufficiency (GC-AI) is made following a normal pituitary magnetic resonance imaging (MRI) scan. With glucocorticoid treatment, her serum sodium normalises.*

## What is glucocorticoid induced adrenal insufficiency?

Adrenal insufficiency is characterised by inadequate glucocorticoid production by the adrenal gland.[1] GC-AI occurs as a result of suppression of the hypothalamic-pituitary-adrenal axis secondary to prolonged exposure to glucocorticoids,[2] and is among the most common types of adrenal insufficiency encountered in clinical practice.[2] In contrast to primary adrenal insufficiency, which is a disease of the adrenal cortex (eg, Addison's disease), mineralocorticoid (aldosterone) secretion remains intact in GC-AI.

## How common is it?

Comprehensive data on the population prevalence of GC-AI are lacking, but given that 1-3% of the population is prescribed systemic glucocorticoids,[2] the prevalence of GC-AI is potentially under reported. GC-AI occurs in up to 20% of patients treated with inhaled corticosteroids (ICS), with a dose dependent relationship seen as ICS dose increases.[3] The risk of GC-AI is higher with oral glucocorticoids. A systematic review and meta-analysis of 74 studies including 3753 patients with various underlying conditions reported that 49% of those with a history of oral glucocorticoid use had evidence of GC-AI either during treatment or at cessation; higher dose and longer duration of treatment were associated with the highest risk.[4]

## Why is it missed?

Adrenal insufficiency often has an insidious onset of non-specific symptoms which overlap with other common conditions, leading to a delay in diagnosis. A lack of awareness by clinicians of the relative frequency of adrenal insufficiency in patients treated with long term (such as >4 weeks) glucocorticoids also contributes to this delay. In a large US questionnaire based study, which included 696 individuals with adrenal insufficiency, of whom 179 had GC-AI,[2] the median duration of symptoms before diagnosis in the whole group was one year, with 66% of individuals with GC-AI visiting more than one physician in that time.[5] Risk factors for GC-AI are presented in box 1, and examples of glucocorticoid doses associated with a risk of developing GC-AI is in table 1. The dose conversion among different types of oral glucocorticoids follows recent guidance[6,7] but differs to values provided in the BNF and some textbooks.

**Box 1: Risk factors for glucocorticoid induced adrenal insufficiency (GC-AI)**

- Exogenous glucocorticoid use at doses equivalent to 5 mg prednisolone for at least four weeks (oral, inhaled, intra-nasal, topical, intra-articular) (table 1)
- Patients treated with 40 mg prednisolone or equivalent for longer than one week
- Repeated short courses of glucocorticoids by oral or other routes (≥ 3 per year)
- Discontinuation of long term glucocorticoids in the past year
- Co-administration of glucocorticoids via multiple routes
- Drug interactions: co-administration of glucocorticoids with drugs that inhibit glucocorticoid metabolism (such as protease inhibitors, antifungals) can cause GC-AI, while addition of drugs that enhance glucocorticoid metabolism (such as some anti-seizure drugs, rifampicin, and St John's Wort (*Hypericum*

This is one of a series of occasional articles highlighting conditions that may be more common than many doctors realise or may be missed at first presentation. To suggest a topic for this series, please email us at practice@bmj.com

*perforatum*)) can precipitate an adrenal crisis in patients with GC-AI already taking glucocorticoids

Table 1 | Examples of glucocorticoid doses associated with risk of secondary adrenal insufficiency when used for four or more weeks[6]

| Route | Dose |
|---|---|
| Oral | Prednisolone ≥5 mg per day<br>Hydrocortisone ≥15 mg per day<br>Dexamethasone ≥500 mcg per day |
| Inhaled/nasal | Beclomethasone >1000 mcg per day<br>Fluticasone >500 mcg per day |
| Topical | Potent or very potent topical glucocorticoids across large area of skin ≥200 g per week |
| Rectal | Potent or very potent topical glucocorticoids ≥30 g per month |

## Why does this matter?

Adrenal crisis is a life threatening emergency, with a mortality rate of 0.5/100 patient years,[3] and is the most serious consequence of a missed diagnosis of GC-AI. The frequent delay in diagnosis results in a high proportion of patients presenting with adrenal crises on first presentation. A retrospective review from the Netherlands found an incidence of 15 adrenal crises per 100 patient years in patients with GC-AI (n=28),[8] although it is likely that cases are under diagnosed and under reported. The features of adrenal crisis are outlined in table 2.

Table 2 | Clinical features and routine laboratory findings in adrenal crisis in patients with glucocorticoid induced adrenal insufficiency (GC-AI)[9]

| Symptoms | Signs | Routine laboratory tests |
|---|---|---|
| Severe weakness | Hypotension | Hyponatraemia |
| Syncope | Abdominal tenderness | Hypoglycaemia |
| Nausea and vomiting | Fever | Hypercalcaemia |
| Abdominal pain | Altered Glasgow coma scale score, delirium | Normocytic anaemia |
| Confusion and impaired consciousness | | Acute renal failure |

## How is it diagnosed?

### Clinical features

Patients with GC-AI lack the classic hallmarks associated with primary adrenal insufficiency, such as hyperpigmentation, hyperkalaemia, and salt cravings.[4] Most prospective studies on GC-AI lack detail on specific clinical features. We recommend that fatigue, general malaise, nausea, weight loss, and hyponatraemia in the context of past glucocorticoid use as outlined in box 1 should raise suspicion of adrenal insufficiency. Patients with GC-AI may paradoxically appear cushingoid, with thin skin, easy bruising, and striae, which result from chronic excess steroid exposure before the recent withdrawal of medication.

### Investigations

The key initial test is a 9 am serum cortisol, taken at least 24 hours since the last glucocorticoid dose. Cut-off values for this test should only be used outside the context of acute illness. No consensus exists on the best cut-off values to use when screening for GC-AI[2 10 11]; in general a 9 am serum cortisol >350 nmol/L (12.7 µg/dL) is safe to exclude the diagnosis.[2] When the diagnosis remains uncertain, continue glucocorticoids and seek advice from an endocrinologist.

### Other considerations

- Do not use random cortisol as a screening test because of the diurnal and pulsatile nature of cortisol secretion.
- Treat acutely unwell patients with suspected GC-AI with glucocorticoid supplementation and revisit the diagnosis once they have recovered.
- Oestrogen containing oral contraceptive pills (OCP) elevate sex hormone binding globulin concentrations, which can produce falsely reassuring cortisol values.[1] Repeat cortisol measurement six weeks after discontinuing the OCP.[6]
- Exclude adrenal insufficiency before a diagnosis of SIADH because the two conditions have similar biochemical results.[12]
- A mildly elevated thyroid stimulating hormone (TSH) and normal free thyroxine may be seen in adrenal insufficiency owing to lack of the normal suppression of thyrotroph cells by cortisol.[12] Do not initiate treatment with thyroxine in this context, as TSH most often normalises with glucocorticoid replacement and the addition of thyroxine in untreated adrenal insufficiency can precipitate or worsen an adrenal crisis.[13]

Glucocorticoid taper and screening for adrenal insufficiency are covered in detail in a recent clinical review by Prete et al.[2]

## How is it managed?

The cornerstone in treatment of GC-AI is glucocorticoid replacement. The correct dose alleviates symptoms of adrenal insufficiency and avoids an adrenal crisis, while minimising complications of over treatment. Hydrocortisone is usually the drug of choice, with the first dose taken immediately on waking. Prednisolone or rarely dexamethasone may be used as alternatives,[7] and modified release formulations of hydrocortisone are also now available, such as plenadren.[14]

Advise patients at greater risk to wear medic-alert jewellery and to carry a steroid emergency card (fig 1) and extra steroids on their person. Educate patients on symptoms of an impending crisis and sick day rules.[7 15] Sick day rules provide patients with guidance on how to adjust steroid doses if they are unwell. Table 3 provides an

example of sick day rules based on guidance from the Society of Endocrinology.[16]

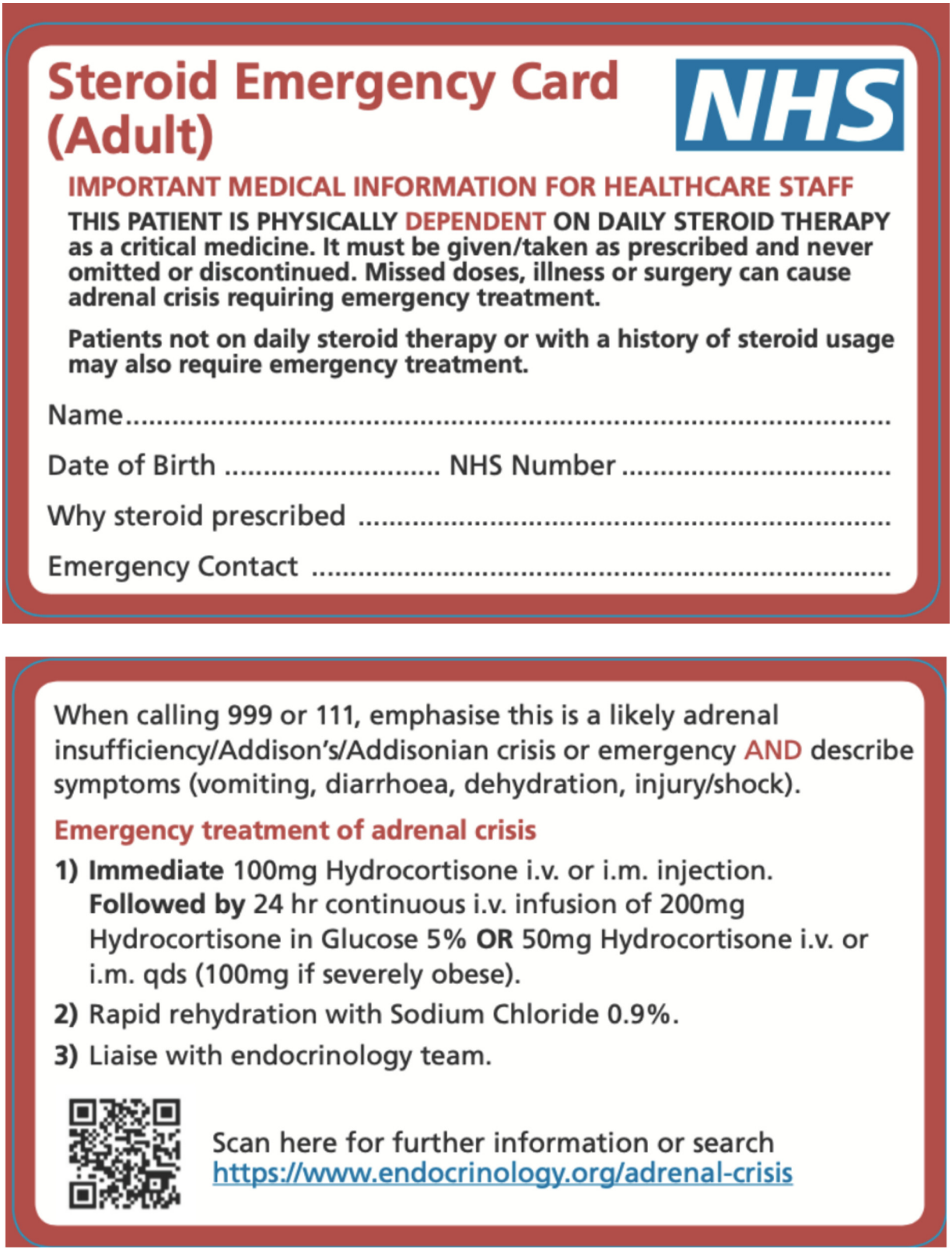


Fig 1 | NHS steroid emergency card

Table 3 | Example sick day rules[16]—advice and practical recommendations for patients on glucocorticoid treatment at risk of GC-AI

| Steroid medication | Normal dose | Unwell with fever | Covid-19 suspected or confirmed |
|---|---|---|---|
| Prednisolone | 3-10 mg daily | Increase to 5 mg twice daily | 10 mg twice daily |
| Prednisolone | 10 mg or more daily | Split daily dose to twice daily | Split daily dose to twice daily, eg, 20 mg daily—take 10 mg twice daily |
| Hydrocortisone | >10 mg daily | 20 mg immediately, then 10 mg every six hours | 20 mg every six hours |
| Other steroid preparation | N/A | Hydrocortisone 20 mg immediately, then 10 mg every six hours | Hydrocortisone 20 mg every six hours |

### Patient information sources

The Society for Endocrinology has published practical guidance for patients on glucocorticoid treatment who are at risk of GC-AI. This includes directions on when and how to take additional glucocorticoids: https://www.endocrinology.org/media/4169/ai-and-exogenous-steroids_patient-information-sheet.pdf .

### How patients were involved in the creation of this article

A draft version of the manuscript was reviewed by a patient with GC-AI, and adapted based on their account of their diagnosis and management.

### Patient experience

The patient with GC-AI highlighted several key issues. Firstly, they felt that in the initial years of glucocorticoid treatment, the clinical focus was primarily on managing the underlying rheumatological condition, with little focus on the implications of long term glucocorticoid treatment. In retrospect, they wished they had been better informed of the symptoms and potential consequences of GC-AI. Before they received a formal diagnosis of GC-AI, they were not aware of "sick day rules." When their prednisolone dose was weaned to 3 mg, symptoms such as joint discomfort and fatigue were attributed to flare of disease rather than adrenal insufficiency, and in retrospect were likely caused by GC-AI. The patient also emphasised the importance of patient education and empowerment in terms of sick day rules management, particularly during intercurrent illness and medical procedures.

### Education into practice

- How would you identify patients in your practice who are at risk of adrenal insufficiency from chronic glucocorticoid therapy?
- What general advice would you give to your patients on long term glucocorticoid therapy? What advice might you give about cessation of glucocorticoid therapy?

### How this article was made

The first author reviewed recent guidance and publications from the Society for Endocrinology, research papers referenced within those publications, and their own archive of relevant references. The authors have been involved in developing protocol for adrenal insufficiency at trust and/or national levels, and this expertise was incorporated in the writing of this manuscript. A patient with GC-AI was invited to review the draft manuscript, and to provide their own patient experience of GC-AI.

Advisers to this series are Anthony Harnden, professor of primary care, Department of Primary Care Health Sciences, University of Oxford, and Kevin Barraclough, School of Social and Community Medicine, University of Bristol.

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