MIL

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This Medicines Information Leaflet is produced locally to optimise the use of medicines by encouraging prescribing that is safe, clinically appropriate and cost-effective to the NHS.

Management of adult patients with adrenal insufficiency and adult patients taking steroid medications during hospitalisation

All patients with adrenal insufficiency are at risk of adrenal crisis. This includes those on long term glucocorticoid steroids (inhaled/oral/topical) not formally diagnosed with adrenal insufficiency.

Adrenal insufficiency is characterised by inadequate glucocorticoid production by the adrenal gland. Primary adrenal insufficiency is a disorder of the adrenal cortex itself, in which glucocorticoid deficiency is typically accompanied by lack of mineralocorticoid secretion. Patients with primary adrenal insufficiency therefore require daily replacement of glucocorticoid (usually with hydrocortisone) and mineralocorticoid hormones (with fludrocortisone).

Secondary and tertiary adrenal insufficiency are caused by disruption of the hypothalamic-pituitary-adrenal (HPA) axis, in which lack of adrenocorticotrophic hormone (ACTH) stimulation leads to isolated glucocorticoid deficiency. Patients with secondary and tertiary adrenal insufficiency require daily glucocorticoid replacement (usually with hydrocortisone) but do not require fludrocortisone, Figure 1.

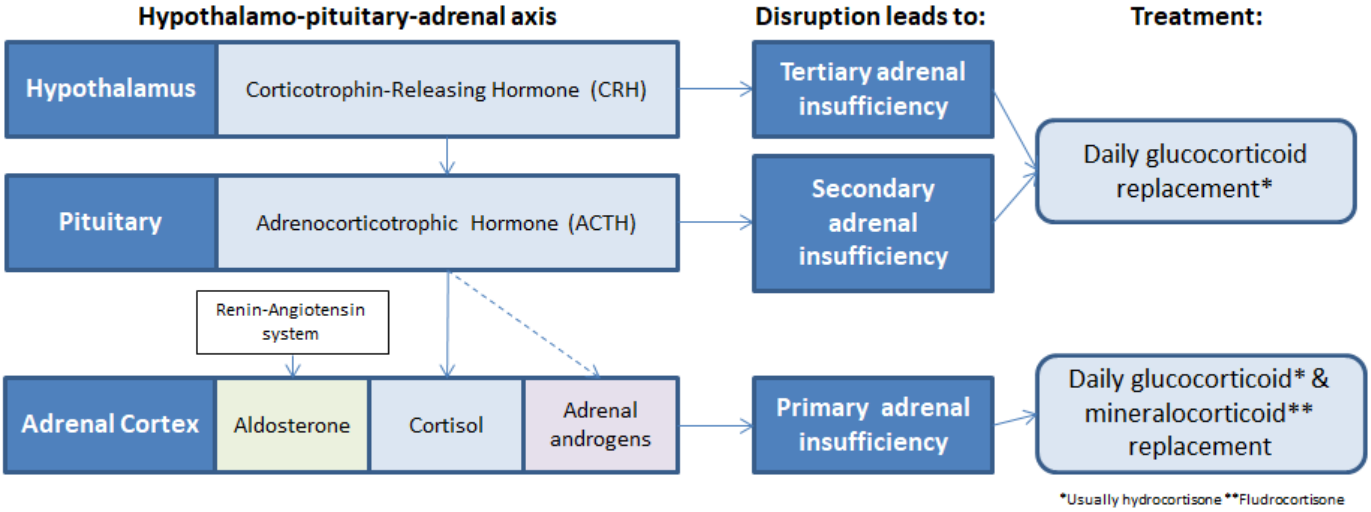


Figure 1. *Physiological control of adrenal hormone secretion*

Table 1. *Causes of Adrenal Insufficiency*

Primary	Secondary	Tertiary
Autoimmune adrenalitis (Addison's Disease) Infections (TB, systemic fungal infections) Malignancy (bilateral metastasis, lymphoma) Congenital adrenal hyperplasia Bilateral adrenal haemorrhage Bilateral adrenalectomy	Tumours (Pituitary tumours, craniopharyngioma, metastases, other) Pituitary surgery Cranial radiation Infiltrative (Neurosarcoidosis, histiocytosis, haemochromatosis) Hypophysitis (Autoimmune, immune checkpoint inhibitors) Post-basal meningitis Pituitary apoplexy, Sheehan's syndrome Subarachnoid haemorrhage, Traumatic brain injury Congenital/Genetic Opiates	Exogenous glucocorticoids (inhaled, nasal, topical, intra-articular)

Steroid-induced adrenal insufficiency

Some patients taking glucocorticoid medicines (steroids) may become steroid dependent due to the development of tertiary adrenal insufficiency (suppression of endogenous cortisol production due to exogenous steroid). Omissions of steroid medicines for these patients can lead to adrenal crisis.

Determining whether someone is at risk of adrenal insufficiency due to steroid medication is a clinical assessment and is the clinician/prescriber's responsibility. People taking steroid medicines in the doses described in Table 2 are likely to be at risk of adrenal insufficiency.

*Table 2: Doses of steroids which can cause adrenal insufficiency**

- Any oral steroid courses of longer than four weeks
- More than 40mg prednisolone daily or equivalent for longer than 1 week, or repeated short courses of oral steroids
- Dexamethasone courses over 10 days
- Any combination of two steroid preparations (including intra-articular, inhaled, topical, nasal, ocular, or injection)
- Concomitant use of CYP3A4 inhibitors**
- Inhaled/nasal steroids doses above:
  - Beclometasone 1000 microgram/day
  - Fluticasone 500 microgram/day

*for more details see Society for Endocrinology recommendations

**including atazanavir, ceritinib, clarithromycin, cobicistat, darunavir, idelalisib, indinavir, itraconazole,ketoconazole, lopinavir, mifepristone, nefazodone, nelfinavir, ombitasvir, posaconasole, ritonavir, saquinavir, voriconazole (full list available through UpToDate)

Adrenal Crisis

Adrenal crisis is an acute life-threatening emergency. It may be the first presentation of adrenal insufficiency or can occur in patients who have been established on replacement glucocorticoid therapy. Common precipitating factors include infection, trauma and surgical procedures or inability to take usual glucocorticoid medicine.

***Table 3:** Clinical Features and routine laboratory findings in Adrenal Crisis*

Symptoms	Signs
Severe weakness	Hypotension
Syncope	Abdominal tenderness
Nausea and vomiting	Fever
Abdominal pain	Hyperpigmentation
Confusion	Altered GCS, delirium
Routine laboratory tests	
Hyponatraemia	Normocytic anaemia
Hypoglycaemia	Acute renal failure
Hypercalcaemia	Hyperkalaemia[#]

[#]in primary adrenal insufficiency

Hydrocortisone IV/IM: Either salt of hydrocortisone can be prescribed (i.e. sodium succinate or acetate) for administration when hydrocortisone IV/IM is mentioned in this MIL, dependent on availability.

Who is at risk of Adrenal Crisis?

1. Patients with established or suspected diagnosis of primary adrenal insufficiency, for example:
   a. Addison's disease,
   b. congenital adrenal hyperplasia (CAH), bilateral adrenalectomy,
   c. adrenal haemorrhage,
   d. following pituitary or adrenal surgery for Cushing's syndrome.
2. Patients with established or suspected diagnosis of adrenal insufficiency due to hypothalamo-pituitary disease who are either on permanent glucocorticoid replacement or require glucocorticoid replacement during illness or stress.
3. Patients taking doses of steroids outlined in Table 2.

Emergency Management of Adrenal Crisis

1. **Hydrocortisone:**
   Give hydrocortisone 100mg IV STAT followed by 200mg over 24 hours as a continuous IV infusion in 250 mL of glucose 5%
   OR
   50mg hydrocortisone every 6 hours IM or IV
   Continue this until discussed with endocrinology and oral conversion deemed appropriate.
2. **Rapid rehydration**
   Use sodium chloride 0.9% (providing no evidence of significant hyponatraemia)
   a) Initial 500ml bolus over 15 minutes, then replacement of any electrolyte deficiencies
   b) Continue rehydration with 3-4 litres over 24 hours with careful monitoring of electrolyte and fluid balance, and blood glucose.
3. **Cardiac monitoring**
4. **Investigate for and treat precipitating cause**
5. **Refer Urgently**
   Refer to endocrinology for advice regarding acute management, switching to oral steroids, and education regarding 'sick day rules' prior to discharge.

Management of Steroid Replacement in patients with adrenal insufficiency

- Glucocorticoids must never be stopped or omitted.
- For patients with adrenal insufficiency, increase normal glucocorticoid dose during times of intercurrent illness as outlined in Table 4.
- Patients on long term oral steroids should have additional doses of steroids as outlined in Table 4.
- Glucocorticoids should be switched to parenteral (IV or IM) if the oral route is not available, for example if nil by mouth, vomiting/diarrhoea.
- For patients taking fludrocortisone with primary adrenal insufficiency, increased doses are not usually required.
- **For steroid replacement during the intra- and post-operative periods, refer to Table 5.**
- Endocrinology may advise a hydrocortisone 100mg IM injection rescue pack to be supplied on discharge for use if the patient becomes acutely unwell.

Table 4. *Management of steroid replacement during intercurrent illness if no evidence of adrenal crisis (1,2)**

Steroid Medication	Normal dose	Unwell with fever or other physiological stress	COVID-19 suspected or confirmed	Severe illness
Prednisolone	Between 3 mg and 10 mg daily	Increase dose to 5mg twice daily	10mg twice daily	Hydrocortisone 100mg IV immediately followed by a continuous infusion of hydrocortisone 200mg over 24 hours or 50mg four times daily IV or IM until severe illness improved. Then switch to oral as per "unwell with fever or other physiological stress" and refer to Endocrinology.
Prednisolone	10 mg or more daily	Split daily dose to twice daily e.g., 20 mg daily → take 10mg twice daily		
Hydrocortisone	Over 10mg daily	20mg immediately, then 10mg every 6 hours	20mg every 6 hours	
Other steroid preparation**	N/A	Hydrocortisone 20mg immediately, then 10mg every 6 hours	Hydrocortisone 20mg every 6 hours	

**Revert to usual dose once illness has improved*
*****S**ee Table 2: Doses of steroids which may cause adrenal insufficiency*

Table 5. *Recommended Steroid Replacement doses for intra-operative and post-operative cover in patients with adrenal insufficiency and patients treated with long term glucocorticoids (1)*

Type of surgery	Intra-operative steroid replacement	Post-operative steroid replacement
Surgery under anaesthesia (GA or regional)	Hydrocortisone 100mg IV on induction, followed by immediate initiation of the post-operative steroid replacement regime.	While patient nil by mouth or for patients with post-operative vomiting, continue the 200mg hydrocortisone daily as a continuous IV infusion or 50mg IV/IM every 6 hours. Resume oral glucocorticoid at pre-surgical therapeutic dose if recovery is uncomplicated. Otherwise, continue increased oral dose glucocorticoid as per **Table 4** 'Unwell with fever or other physiological stress' column for up to one week according to severity of complications.
Bowel procedures requiring bowel preparation with laxatives/ enema	**For bowel prep under clinical supervision:** • Consider intravenous fluids and hydrocortisone 50mg IM or IV every 6 hours during bowel preparation (Especially for patients taking fludrocortisone and/or with diabetes insipidus - discuss with endocrinology) **At the start of the procedure:** • Hydrocortisone 100mg IV or IM as single dose	Resume increased oral dose glucocorticoid (**Table 4** "Unwell with fever or other physiological stress") doses for 24 hours
Labour and vaginal delivery	Hydrocortisone 100mg IV on induction, followed by immediate initiation of the 200mg hydrocortisone daily as a continuous IV infusion or 50mg IV/IM every 6 hours.	Resume oral stress glucocorticoid doses (**Table 4**) for 48 hours
Caesarean section	See surgery under anaesthesia	See surgery under anaesthesia

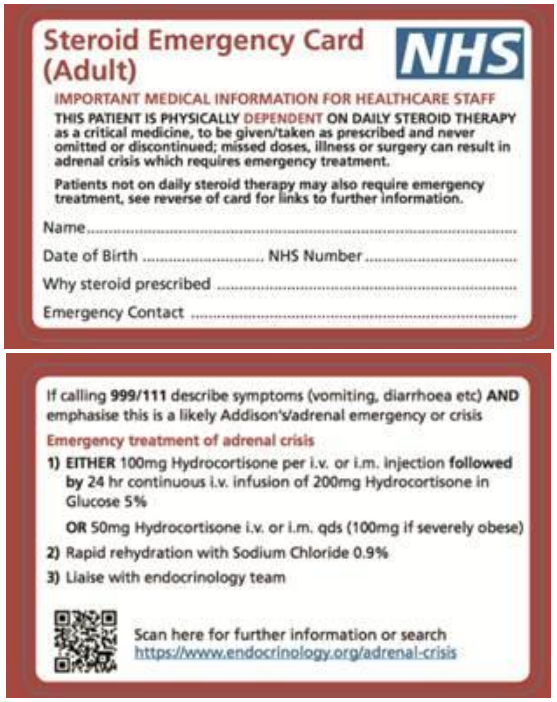
NOTE: Patients who are 'nil by mouth' from midnight pre-operatively can usually take their morning glucocorticoid with a sip of water – please check with surgeon/anaesthetist. If not, they should be given parenteral (IV/IM) glucocorticoid while awaiting surgery.

Red Steroid Emergency Card

The Red Steroid Emergency Card has been introduced in England in response to the identification of incidents reported nationally around issues with steroid replacement therapy that resulted in injury or death.

The Red Steroid Emergency Card must be given to all patients at risk of adrenal insufficiency following the national patient safety alert. This includes inpatients, outpatients, emergency admissions, day cases, ambulatory admissions and at pre-operative assessment. Counselling and education must be provided to ensure the patient understands the importance of the steroid treatment and what to do when feeling unwell.

This card contains suggested wording that patients should use when accessing emergency medical care to highlight that they are at risk of adrenal crisis. The card also contains a reminder of the doses of additional steroids required during emergency medical treatment.



Cards can be ordered by clinical areas or obtained via the pharmacy dispensaries. To request from pharmacy, add a note in the special instructions section of the steroid prescription or contact the pharmacy via the ward pharmacist bleep or telephone the local dispensary. For areas who wish to order the cards directly, the ordering information is available here.

The Blue Steroid Treatment Card is still provided to relevant patients taking long term courses of steroids to highlight that these must not be stopped suddenly.

Some patients may express concerns about the risks and benefits of their steroid treatment, particularly if given the red Steroid Emergency Card by someone other than the doctor who initiated the medicine or if this hasn't been previously explained. These patients should be signposted to their clinical team (Specialist Nurse/Consultant) who are responsible for the steroid therapy or their GP for more involved discussions and supplies of any oral hydrocortisone which may be required (as per Table 4).

The Red Steroid Emergency Card must be given either directly by the prescriber or a supply arranged through pharmacy. It is the responsibility of the treating clinician or non-medical prescriber to identify the need for a Steroid Emergency Card. Cerner Millenium ePMA will provide an alert highlighting that the patient is prescribed steroids medicines at a dose that could lead to adrenal insufficiency, and will prompt the issue of a Red Steroid Emergency Card.

The Endocrinology Team are available via Switchboard to discuss any complex cases if necessary.

Prepared by:

Aoife Garrahy, Post CCT Fellow in Endocrinology

Aparna Pal, Consultant Endocrinologist

Jeremy Tomlinson, Consultant Endocrinologist

Judith Bailey and Cate Leon, Joint Lead Medicine Safety Pharmacists

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