Guidance for the prevention and emergency management of adult patients with adrenal insufficiency

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Guidance for the Prevention and Emergency Management of Patients with Adrenal Insufficiency.

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Guidance for the Prevention and Emergency Management of Patients with Adrenal Insufficiency.

Abstract:

Adrenal insufficiency (AI) is an often unrecognised endocrine disorder, which can lead to adrenal crisis and death, if not identified and treated. Omission of steroids in patients with AI, particular during physiological stress such as an intercurrent illness or surgery, can also lead to an adrenal crisis. The National Reporting and Learning System (NRLS) identified 78 incidents including two deaths and six incidents of severe harm to patients in a recent four-year period. This guidance will go through causes of adrenal insufficiency, groups at risk of an adrenal crisis, emergency management and management for surgical procedures. A new NHS Steroid Emergency Card has been developed to be carried by patients at risk of adrenal crisis. We hope the new emergency card and this guidance will increase awareness of the need to start steroids promptly in patients at risk of an adrenal crisis, particularly when presenting in the emergency department or to acute medicine teams, undergoing surgery, or invasive procedures.

Key words:

Adrenal insufficiency, adrenal crisis, emergency management, steroids.

Key Practice Points:

- Omission of steroids in patients with adrenal insufficiency/steroid dependence, particular during physiological stress such as an intercurrent illness or surgery, can lead to an adrenal crisis, and death.
- All patients with adrenal insufficiency (AI)/steroid dependence are at risk of an adrenal crisis during intercurrent illness or an invasive procedure/surgery.
- Patients with AI include patients with primary adrenal insufficiency such as Addison's disease and congenital adrenal hyperplasia, and hypothalamo-pituitary damage from tumours or surgery.
- Patients taking exogenous steroids are also at risk of AI. Patients taking prednisolone 5mg/day or equivalent for 4 weeks or longer across all routes of administration (oral, topical, inhaled, intranasal) should be issued with an emergency steroid card..
- Inhaled beclamethasone >1000mcg/day, fluticasone >500mcg/day are at risk of adrenal insufficiency due to hypothalamo-pituitary axis suppression and should be issued with an emergency steroid card.
- Patients thought to be having an adrenal crisis should be treated promptly with 100 mg Hydrocortisone per i.v. or i.m. injection, followed by 200mg Hydrocortisone/24h continuous iv infusion in Glucose 5%/24h , or 50mg 6 hourly i.m. (or i.v.). and intravenous fluid (sodium chloride 0.9%).
- Emergency treatment should not be delayed whilst waiting to confirm a diagnosis of adrenal insufficiency.
- A new NHS Steroid Emergency Card will be launched shortly to be carried by patients at risk of adrenal crisis.
- All Health Care Professionals (HCP) should be aware of the patient groups at risk of an adrenal crisis
- All doctors should be aware of the need to start steroids promptly in patients at risk of an adrenal crisis, either at replacement or stress doses, particularly when presenting in the emergency department or to acute medicine teams, undergoing surgery, or invasive procedures.
- Patient education is a key part of management. Patient resources are available on the Addison's Disease Self Help Group (https://www.addisonsdisease.org.uk) and The Pituitary Foundations' websites (https://www.pituitary.org.uk).

Background

Adrenal insufficiency (AI) is an often unrecognised endocrine disorder, which can lead to adrenal crisis and death, if not identified and treated.[1] Omission of steroids in patients with AI, particular during physiological stress such as an intercurrent illness or surgery, can also lead to an adrenal crisis. The National Reporting and Learning System (NRLS) identified 78 relevant incidents including two deaths and six incidents of severe harm to patients in a recent four-year period. Multiple themes were present including:

- failure to implement or inadequate peri-operative plans that take into account the patient's need for increased steroid doses during surgical stress
- inadequate admission and discharge medication-reconciliation practices
- omitted or delayed administration of prescribed doses, including when ward stock medicines were unavailable; alternative routes of administration not used when patients were nil by mouth
- emergency hydrocortisone injections not being available in ambulances
- inappropriate 999/111 response categorisation leading to treatment delays.

Substantial resources exist, including clinical guidance.[2-5] However, clinical staff are not always aware of the risk of adrenal crisis, do not refer to the available literature and guidelines or implement the correct clinical response should one occur. In view of this there is a need for a change in the way all health care professionals are alerted to patients who have AI and are at risk of an adrenal crisis. This guidance is primarily for the management of adults, but for completeness we have added recommendations for managing children.

Causes of Adrenal Insufficiency.

Commonest causes of primary AI include Addison's disease, congenital adrenal hyperplasia, bilateral adrenalectomy and adrenal haemorrhage (Table 1). Causes of secondary AI are pituitary disease, pituitary tumours and their treatment (surgery and radiotherapy), and, also termed tertiary AI, hypothalamic-pituitary-adrenal axis (HPA) suppression from exogenous steroids and, more rarely, treatment of primary brain or nasopharyngeal tumours with radiotherapy when the hypothalamus and/or pituitary is included in the treatment field. Hypothalamo-pituitary disorders account for 60% of patients, with AI whilst 40% have primary adrenal failure due to Addison's disease (0.9-1.4 per 10,000) or congenital adrenal hyperplasia (0.7-1.0 per 10,000). Clinical findings of patients presenting with AI and laboratory investigations are summarised in Supplementary Tables 1 and Table 2.[3] If AI is suspected, then prompt treatment should not be delayed by performing or waiting for the results of diagnostic

testing. This can be performed at a later date when the patient is clinically stable. There are no adverse consequences of initiating life-saving hydrocortisone treatment.

Glucocorticoid preparations.

Glucocorticoid preparations include hydrocortisone (=cortisol), prednisolone and dexamethasone. They vary in their immunosuppressive and metabolic properties; 10 mg hydrocortisone is roughly equivalent to 2.0 mg prednisolone and to 0.2 mg dexamethasone. All have excellent oral bioavailability, with rapid absorption. Patients with AI are treated with physiological doses of glucocorticoids, predominantly hydrocortisone (average 15-25mg/day in divided doses), prednisolone (3-5mg/day) and rarely dexamethasone (0.25-0.5mg/day). Patients with primary AI may also have aldosterone deficiency and, therefore, require fludrocortisone replacement.

Many more patients other than those with adrenal and hypothalamic-pituitary causes of AI are receiving glucocorticoids as treatment for other medical conditions. Seven per 1000 population are prescribed long-term oral glucocorticoid therapy, approximately 100 times the number with intrinsic deficiency, creating a large population at risk of adrenal crisis.[6] Prescribed glucocorticoid therapy, across all routes of administration (oral, inhaled, topical, intranasal, intra-articular), can cause suppression of the hypothalamo-pituitary-adrenal (HPA) axis.[7-10] Oral glucocorticoids cause HPA axis suppression at a dose of prednisolone 5mg/day or even less. [12] Inhaled corticosteroid therapy is very common, and whilst is has been claimed not to endanger the functioning of the HPA axis when administered within recommended dose ranges. Budesonide and ciclesonide are approximately equipotent with beclomethasone (BDP), while fluticasone propionate (FP), mometasone and ultrafine particle BDP-HFA inhalers (Qvar® and Fostair®) are twice as potent as standard BDP inhalers. Recent evidence has shown that partial suppression of the adrenal response to ACTH is common.[11,13] Furthermore, it can occur at commonly prescribed high doses and in a dose-dependent manner. Guidance exists from the London Respiratory network and others in this regard advising carrying a steroid card at doses >1000mcg for beclomethasone, and >500mcg/day for fluticasone (https://www.networks.nhs.uk/nhs-networks/london-respiratory-network/key-documents/responsible-respiratory-prescribing/LRT%20Inhaled%20steroid%20safety%20card.pdf; https://www.rightbreathe.com).

Drugs affecting Glucocorticoid metabolism

In addition, certain drugs affect glucocorticoid metabolism. The commonest group are those affecting the activity of the drug- xenobiotic-metabolising enzyme CYP3A4. Anticonvulsants, rifampicin, topiramate and mitotane are well known to increase downstream metabolism of cortisol through induction of CYP3A4 activity. [13,14] If a drug induces CYP3A4 activity and is

administered together with exogenous glucocorticoids, which suppress the HPA axis suppression, stopping the exogenous glucocorticoids but continuing the CYP3A4-inducing drug can result in acute AI , i.e. adrenal crisis.

Similarly, drugs like antifungals such as itraconazole and voriconazole, which delay steroid metabolism by inhibiting CYP3A4 activity, can result in iatrogenic Cushing's. [15,16] Antiretroviral therapy (protease inhibitors eg: ritonovir) can also inhibit glucocorticoid metabolism, leading to iatrogenic Cushing's Syndrome.[17] This has also been reported for steroid eye drops, Fluticasone, Triamcinolone and Budesonide.[18] Hence, if these CYP3A4-inhibiting drugs are stopped, the HPA axis of these patients is suppressed and they can experience adrenal crisis, which can be prevented by initiation of hydrocortisone replacement.

There is currently little evidence to support increased doses of glucocorticoids in all patients on drugs affecting CYP3A4 but clinicians should have a high degree of clinical suspicion and give stress doses of hydrocortisone if there is any concern with regards to the development of an adrenal crisis during an intercurrent illness or a procedure. [19]

Adrenal Crisis

An adrenal crisis is a medical emergency. All steroid-dependent patients are at risk of adrenal crisis. White and Arlt reported that 47% of 275 patients with Addison's disease in the UK had had at least one admission with adrenal crisis.[20] Others have reported an incidence of adrenal crisis in primary AI of 8.3 crises in 100 patient years and 3.6-5.2 per 100 patient years in secondary AI.[21,22] Moreover, one in every 6-12 patients with AI will have an adrenal crisis within the next 12 months whilst one in 200 patients will die from such a crisis with 5,526 to 10,647 expected deaths from adrenal crises in the coming decade in the EU, if the current situation prevails.[23] Commonest causes of crisis in known AI are gastrointestinal illness 23%, other infections 25%, peri-surgery 10% and physiological stress/pain 9%.[20]

Who should be considered to be at risk of acute adrenal insufficiency (=adrenal crisis)?

- Patients with an established or suspected diagnosis of primary AI (eg Addison's disease and Congenital Adrenal Hyperplasia (CAH) bilateral adrenalectomy and adrenal haemorrhage)
- Patients with an established or suspected diagnosis of AI due to hypopituitarism due to hypothalamo-pituitary disease who are either on permanent glucocorticoid replacement or require glucocorticoid replacement during illness or stress such as a surgical procedure.
- Patients taking exogenous glucocorticoid therapy equivalent to or exceeding a dose of prednisolone 5mg/day for 4 weeks or longer across all routes of administration (oral,

topical, inhaled, intranasal, intra-articular) as they are likely to have suppressed HPA function (= tertiary AI)

- Patients taking more than 40mg prednisolone of equivalent for longer than 1 week or repeated courses of short oral doses
- Patients taking a course of oral glucocorticoid within 1 year of stopping long-term therapy

All patients, but in particular pregnant patients considered at risk of or with suspected incipient adrenal crisis should be treated immediately; a single high dose hydrocortisone administration has no adverse effects on the developing fetus (and is mostly inactivated in the placenta), but not treating rapidly could result in the loss of life of the mother and the unborn child.

Which patients require additional investigations to clarify risk of adrenal crisis?

If a diagnosis of acute AI is suspected on clinical grounds, glucocorticoids in a dose appropriate for major stress should be given immediately as there are no adverse effects from short-term administration of glucocorticoids. No additional testing is required in the acute situation.

Management of adrenal crisis in adults (Figure 1)

An adrenal crisis is a medical emergency. Management of adrenal crisis includes prompt administration of glucocorticoids, usually hydrocortisone, and crystalloid fluid. If an adrenal crisis is being considered in a patient not previously known to have AI, treatment should not be delayed whilst trying to make a diagnosis. Investigations can be initiated once the patient is clinically stable.[3]

Emergency treatment of adrenal crisis

- 100 mg Hydrocortisone per i.v. injection, followed by 200mg Hydrocortisone/24h continuous iv infusion in Glucose 5%/24h , or 50mg 6 hourly i.v*.
- Rapid rehydration with sodium chloride 0.9% providing no evidence of hyponatraemia:
    - Resuscitation with 500ml fluid bolus of sodium chloride 0.9% over 15 minutes and then replacement of any fluid and/or electrolytes deficits.
    - Rehydration (3-4 litres of sodium chloride 0.9% solution in 24 hours (initially 1litre/h), then drinking ad libitum)
- Cardiac monitoring (if necessary transfer to the intensive care unit for monitoring)
- Refer to endocrinology for further advice on diagnosis, starting regular oral steroids or tapering steroids, education regarding Sick Day Rules prior to discharge.

More detailed information can be found at http://www.endocrinology.org/adrenal-crisis
See also NICE Guidance Intravenous fluid therapy in adults in hospital
https://www.nice.org.uk/guidance/cg174/chapter/1-recommendations

***Note:**

1. In severe obesity consider substituting 50mg hydrocortisone with 100mg hydrocortisone

2. Whilst it is recommended hydrocortisone 50mg every 6 hours is given i.m., hydrocortisone can be given i.v. if patients are anticoagulated or clinically indicated.

Particular care is required in patients who have diabetes insipidus as well as AI, which is usually patients with AI due to hypothalamic-pituitary disease. This is because cortisol is required to excrete a water load. Adults and children with AI and diabetes insipidus related to hypothalamic/pituitary disease who are treated with D-amino D-arginine vasopressin (DDAVP) administration are at risk of uncontrolled diabetes insipidus, if doses of DDAVP are omitted, or hyponatraemia, if excess fluid is given. Strict fluid balance with adequate cortisol replacement is mandatory to avoid hyponatraemia, which may otherwise be associated with significant morbidity. DDAVP should be continued as prescribed and advice of Endocrinologist sought. Strict fluid balance with adequate cortisol replacement is mandatory to avoid hyponatraemia, which may otherwise be associated with significant morbidity. Further Guidance for emergency management is available from the Society for Endocrinology website.[24]

Recommended clinical treatment for patients with adrenal insufficiency when undergoing surgery or an invasive procedure.

Surgery and sepsis are major physiological stressors, activating the hypothalamo-pituitary-adrenal axis to produce glucocorticoid, the major one being cortisol[25]. Patients with AI of any cause are unable to mount an endogenous cortisol stress response to surgery or invasive procedures, and subsequent hypotension and shock can be fatal. Therefore, all patients with AI of any cause, or considered at risk of AI, are at risk of adrenal crisis, and should be given stress doses of exogenous glucocorticoids for a surgical or invasive procedure as per the Guidelines from the Association of Anaesthetists, the Royal College of Physicians and the Society for

Endocrinology to maintain as near physiological concentration of cortisol as possible. (Tables 2 and 3).[25, 26]

Patients with primary AI who are additionally aldosterone deficient may be susceptible to post-operative fluid balance issues and hyponatremia. A tendency to water retention and hyponatraemia induced by anti-diuretic hormone is very common after surgery, and thus patients with insufficient aldosterone production will be particularly susceptible to hyponatraemia.

All patients at risk of adrenal crisis should be given extra glucocorticoid when undergoing surgery or an invasive diagnostic procedure. One suggested exception is for patients on supraphysiological exogenous steroids undergoing colonoscopy in whom it is suggested to continue their usual dose and have intravenous hydrocortisone if they are expected to remain nil by mouth for a prolonged period of time. If in doubt about the need for stress dose steroids, they should always be given without delay, as there are no long-term adverse consequences of short-term corticosteroid administration.

Patients with a long-standing diagnosis of AI are often well-informed about their disease. All HCP involved in a patient's care should enquire closely about the patient's history of steroid self-management, any previous episodes of adrenal crisis, and how practiced they are at medication adjustments for illness, injury or postoperative recovery. As far as possible other teams should liaise with the patient's endocrinologist when planning scheduled surgery, and when caring for post-surgical cases.

All AI patients, both adults and children, should have 'first on the list' priority in order to minimise fasting or dehydration, which they tolerate poorly. Children with AI are at particular risk of hypoglycaemia when fasted and thus should have regular capillary blood glucose checks. No child with adrenal insufficiency should be fasted for more than 6 h. After surgery, capillary blood glucose should be checked every 2 h until enteral intake is resumed.

Management of Patients with Adrenal Insufficiency and Intercurrent Illness- 'sick day rules' (Figure 2)

There is also a need to highlight the importance of stress dose steroids for all patients at risk of adrenal crisis during an intercurrent illness, as again they are unable to mount a stress response by increasing endogenous glucocorticoid production. Patient education is a critical part of management of patients with AI and they should be taught 'sick day rules'

(Supplementary information) to double oral glucocorticoid if there are unwell. If on a low dose hydrocortisone replacement such as 15mg/day or less, consider total of 40mg a day: 20mg rising 10mg lunchtime, 10mg teatime. Patients on long acting hydrocortisone preparations such as plenadren should take the more rapidly absorbed hydrocortisone during an intercurrent illness. During the Corona Virus Pandemic it become clear that higher doses of hydrocortisone than usual are needed to prevent adrenal crisis for patient who become unwell Covid-19[27]. Patients with AI should carry an NHS Emergency Steroid Card, may also wear a medic alert bracelet or necklace and use mobile phones to create Medical ID for use in an emergency. Patients with AI are particularly at risk from diarrhoea and vomiting illnesses, as they are unable to absorb their oral steroids. Patients with established AI and their carers/family members should be educated about the risks of intercurrent illness and trained in (self) administration of 100mg i.m. hydrocortisone (efcortisol or solucortef) and if the vomiting and diarrhoeal illness persists to attend their local hospital as they will need parenteral hydrocortisone and intravenous fluids without delay. Patients and their relatives or carers can be taught how to self-inject by their endocrine CNS.

Glucocorticoid replacement during stress

There is a group of patients, usually with secondary or tertiary AI including treatment with exogenous steroids or other drugs such as high dose steroid inhalers, or antiretroviral medication, who, after assessment by an endocrinologist, are found to have suboptimal cortisol response do not need regular glucocorticoid replacement. These patients are advised to inform other HCPs that they come into contact with in emergency situations, they require hydrocortisone during an intercurrent illness and to have steroid cover for surgery or invasive procedures, and carry an NHS Emergency Steroid Card.

A pragmatic approach to glucocorticoid replacement during major stress is required, considering the evidence available; blanket recommendations would not be appropriate, and it is essential for the clinician to remember hydrocortisone stress dose cover is administered in addition to the usual glucocorticoid dose in patients with HPA suppression due to exogenous glucocorticoid treatment.

Children

An example of guidance for children is given in figure, shared by the Endocrinology team at Great Ormond Street Hospital (Supplementary figure 1). For intercurrent illness the patient should take double the normal dose of hydrocortisone for 48h, and this should then be reduced to standard hydrocortisone doses once the child becomes well again. Children with AI are at

particular risk of hypoglycaemia especially overnight and some centres recommend an additional dose of hydrocortisone at 4am when unwell. Emergency treatment of adrenal crisis in hospital should follow surgical guidelines (Supplementary table 3).

Increasing awareness in healthcare professionals and patients of adrenal crisis and it's avoidance

Two deaths and sixteen incidents of severe harm to patients with AI in a 2-year period have been reported to national learning systems recently. Any harm or death from acute AI is not acceptable and preventable in most, if not all cases. Many healthcare professionals care for patients with AI, including GPs, acute medicine teams, emergency departments, medical specialities, surgeons and anaesthetists to name but a few. We all need to improve the management of patients with adrenal insufficiency. Patients and HCPs should have information readily available to them which includes:

- Background information for professionals and patients on the prevention and emergency treatment of adrenal crisis
- The use of the NHS Steroid Emergency Card, Medic Alert bracelets/necklaces, mobile phone medical ID.
- Education on sick day rules
- The regular provision of Hydrocortisone Emergency Self Injection Kits and training of patients and carers/families in its use
- Emergency contact telephone number of their regular endocrine care team

Patient resources are available on the Addison's Disease Self Help Group (https://www.addisonsdisease.org.uk) and The Pituitary Foundations' websites (https://www.pituitary.org.uk). Additionally there is a Youtube video (Adrenal Crisis: when to give an emergency injection https://www.youtube.com/watch?time_continue=12&v=NpIEMlschTg). Emergency hydrocortisone I.M. should be added to patient's prescription for patients with primary adrenal insufficiency, and those with hypothalamo-pituitary disease for emergency use (table 4b). In addition patients should be issued with extra oral hydrocortisone for emergency use. Patients can register with their local ambulance trust (https://www.nhs.uk/servicedirectories/pages/nhstrustlisting.aspx) so that they are 'red flagged' as potentially needing emergency parenteral hydrocortisone. ADSHG and the Pituitary Foundation websites have further information on how to do this.

This document and the others listed are a source of valuable information for HCP. Some secondary and tertiary care centres are developing automatic alert systems in their institutions' electronic patient records to ensure a patient with AI is clearly flagged upon admission and receives appropriate hydrocortisone cover if clinically unwell or undergoing surgery. Patients can be encouraged to keep clinic letters with them as images on their smart phones, or use patient held medical records to inform HCP as appropriate.

New NHS Steroid Emergency Card

A new NHS Steroid Emergency Card has been developed (Figure 3). It will be held by patients at risk of adrenal crisis (Table 4a) and includes a management summary for the emergency treatment of adrenal crisis alongside a link to the Society for Endocrinology emergency management guidelines. It can be issued by any HCP looking after patients with AI. Ordering will be through usual NHS Business Service routes. If there is any doubt as to who should carry an Steroid Emergency Card, prompt liaison with the local endocrinology team would be advised. In addition, if there is uncertainty about a diagnosis of AI in any patient, this should be discussed with the local endocrinology team. This guidance and the NHS Steroid Emergency Card should prompt all healthcare professionals to consider adrenal crisis in patients carrying the card, initiate appropriate management for surgery or invasive procedures and treat patients rapidly and appropriately when presenting as an emergency. In this way, avoidable deaths in patients with AI will hopefully be a thing of the past.

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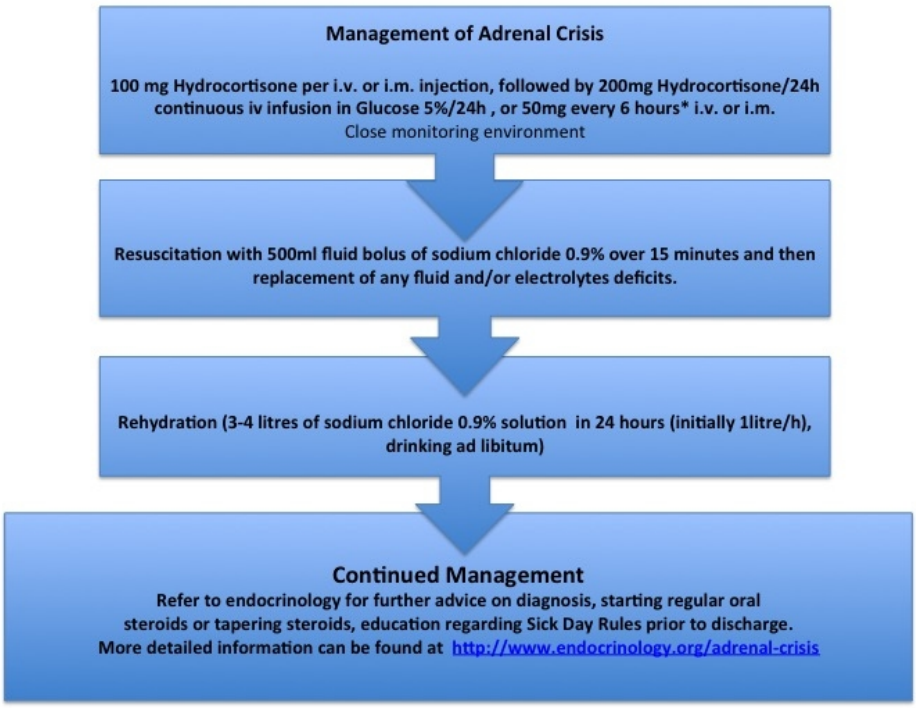
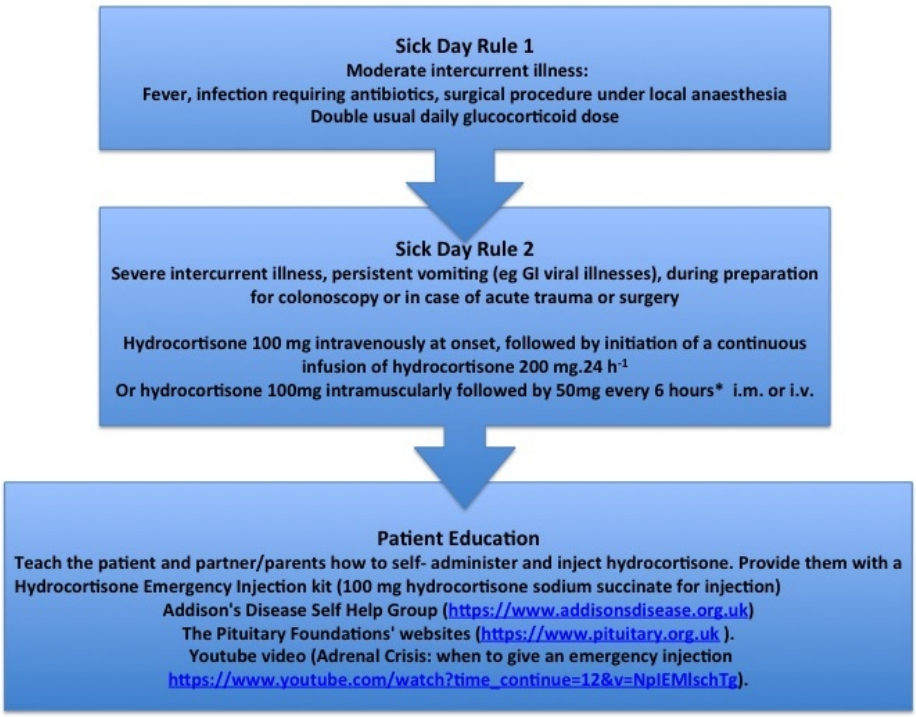


Figure 1: Emergency Management of adrenal crisis

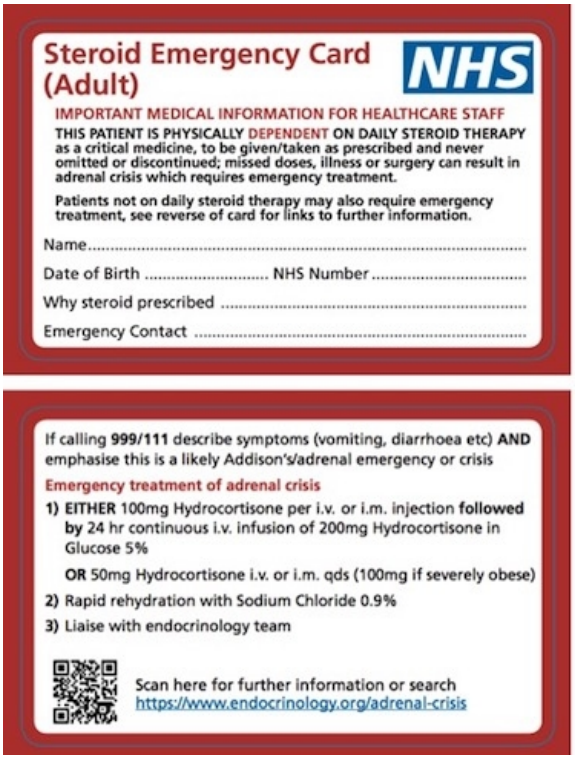
Note:
1. In severe obesity consider substituting 50mg hydrocortisone with 100mg hydrocortisone
2. Whilst it is recommended hydrocortisone 50mg every 6 hours is given i.m., hydrocortisone can be given i.v. if patients are anticoagulated or clinically indicated.

254x190mm (72 x 72 DPI)



Caption : Figure 1: Emergency Management of adrenal crisisNote: 1. In severe obesity consider substituting 50mg hydrocortisone with 100mg hydrocortisone2. Whilst it is recommended hydrocortisone 50mg every 6 hours is given i.m., hydrocortisone can be given i.v. if patients are anticoagulated or clinically indicated.

254x190mm (72 x 72 DPI)



The new NHS Emergency Steroid Card

230x172mm (72 x 72 DPI)

Table 1

Commonest Causes of adrenal insufficiency	
Primary adrenal insufficiency	
Autoimmune/Addison's Disease	
APS Type 1	(APECED)
APS Type 2	
Infections: adrenalitis	TB, HIV/AIDS, CMV, Fungal, syphilis,
Bilateral adrenal haemorrhage	Adrenal Haemorrhage sepsis, anticoagulants, anti-phospholipid syndrome
Bilateral adrenal metastases	primarily lung, stomach, breast, colon
Bilateral adrenal infiltration	primary adrenal lymphoma amyloidosis, haemochromatosis
Bilateral adrenalectomy	
Drug Induced	anticoagulants, adrenal enzyme inhibitors: mitotane, ketoconazole, itraconazole, voriconazole, metyrapone, etomidate, aminoglutethimidie, phenobarbital, phenytoin, rifampicin
Genetic disorders	Congenital adrenal hyperplasia (commonest cause in children) adrenoleukodystrophy
Secondary adrenal insufficiency-pituitary disorders	
Pituitary tumours	eg. adenoma, cysts, craniopharyngioma, ependymoma, meningioma, pituitary metastases
Pituitary Surgery	
Pituitary Irradiation	
Trauma	
Infections/infiltration	lymphocytic hypophysitis, sarcoidosis, histiocytosis X, haemochromatosis, TB
Pituitary apoplexy	
Sheehan's syndrome	
Genetic disorders	transcription factors involved in pituitary development
Tertiary adrenal insufficiency	
Hypothalamic tumours	eg. craniopharyngiomas, germinomas, meningioma's
Hypothalamaic surgery	primary brain tumours or nasopharyngeal tumours
Hypothalamic irradiation	primary brain tumours or nasopharyngeal tumours
Infections/infiltration	lymphocytic hypophysitis, sarcoidosis, histiocytosis X, haemochromatosis, TB
Trauma	traumatic brain injury, particularly base of skull fracture
Cushing's disease/syndrome	
Drug induced	Glucocorticoid therapy (any route), mifepristone, chlorpromazine, imipramine

Adapted from Charmandari 2014 [26]

Table 2 Recommended doses for intra- and postoperative steroid cover in adults with primary including CAH, and hypothalamo-pituitary disease. [26]

	Intra-operative steroid replacement	**Postoperative steroid replacement**
Surgery under anaesthesia (general or regional), including joint reduction, endoscopy, IVF egg extraction	Hydrocortisone 100 mg intravenously on induction, followed by immediate initiation of a continuous infusion of hydrocortisone 200 mg.24 h^{-1} Alternative hydrocortisone 50mg i.m. 6 hourly	Hydrocortisone 200 mg.24 h^{-1} by intravenous infusion while nil by mouth or for patients with postoperative vomiting. Alternative hydrocortisone 50mg i.m. 6 hourly Resume enteral glucocorticoid at pre-surgical therapeutic dose if recovery is uncomplicated. Otherwise continue double oral dose for up to a week
Bowel procedures requiring laxatives/enema.	Bowel prep under clinical supervision. Consider intravenous fluids and injected glucocorticoid (hydrocortisone 50mg i.m. or i.v. 6 hourly) during preparation, especially for fludrocortisone or vasopressin-dependent patients. Hydrocortisone 100 mg intravenously or intramuscularly at the start of procedure	Resume enteral– double hydrocortisone doses for 24h

Labour and vaginal delivery	Hydrocortisone 100 mg intravenously at onset of labour, followed by immediate initiation of a continuous infusion of hydrocortisone 200 mg.24 h^{-1} Alternative: hydrocortisone 100mg intramuscularly followed by 50mg every 6 hours i.m.	Resume enteral – double hydrocortisone doses for 48 h
Caesarean section	See surgery under anaesthesia	

Table 3: Recommended doses for intra- and postoperative steroid cover in adults receiving adrenosuppressive doses of steroids (high dose inhaled steroids, or those on combined inhaled steroids and interfering drugs; prednisolone equivalent ≥5mg for 4 weeks or longer)

	Intra-operative steroid replacement	**Postoperative steroid replacement**
Major surgery	Hydrocortisone 100 mg intravenously at induction, followed by immediate initiation of a continuous infusion of hydrocortisone at 200 mg.24h^{-1} Alternative hydrocortisone 50mg i.m. 6-hourly Alternatively, dexamethasone 6––8 mg intravenously, if used, will suffice for 24h	Hydrocortisone 200 mg.24 h^{-1} by intravenous infusion while nil by mouth. Alternative hydrocortisone 50mg i.m.. 6-hourly Resume enteral glucocorticoid at pre-surgical therapeutic dose if recovery is uncomplicated. Otherwise continue double oral dose for 48 h
Body surface and intermediate surgery	Hydrocortisone 100 mg, intravenously at induction, followed by immediate initiation of a continuous infusion of hydrocortisone 200 mg.24 h^{-1} Alternative hydrocortisone 50mg i.m. 6-hourly Alternatively, dexamethasone 6––8 mg intravenously, if used, will suffice for 24h	Double regular glucocorticoid dose for 48 hours, then continue usual treatment dose
Bowel procedures requiring laxatives/enema	Continue normal glucocorticoid dose. Equivalent intravenous dose if prolonged nil by mouth. Treat as per primary adrenal insufficiency (see above) if concerned about HPA axis function, and risk of adrenal insufficiency	
Labour and vaginal delivery	Hydrocortisone 100 mg intravenously at onset of labour, followed by immediate initiation of a continuous infusion of hydrocortisone 200 mg.24 h^{-1} Alternative: hydrocortisone 100mg intramuscularly followed by 50mg every 6 hours i.m.	

Caesarean section	See major surgery

Note:

1. In severe obesity consider substituting 50mg hydrocortisone with 100mg hydrocortisone

2. Whilst it is recommended hydrocortisone 50mg every 6 hours is given i.m., hydrocortisone can be given i.v. if patients are anticoagulated or clinically indicated.

Table 4a: Patients in whom new emergency steroid card should be given

Primary adrenal insufficiency	All causes Commonest causes: Addison's disease, congenital adrenal hyperplasia, bilateral adrenalectomy and adrenal haemorrhage
Pituitary/hypothalamic disease	Patients with hypothalamo-pituitary dysfunction known to be steroid dependent Patients with hypothalamo-pituitary advised to take steroids for intercurrent illness
Other causes:	Patients on exogenous steroids prednisolone 5mg/day or more dexamethasone 0.5mg/day or more hydrocortisone 15mg/day or more inhaled steroids Fluticasone >500mcg/day Beclomethasone >1000mcg/day Nasal steroids >1000mcg/day Drugs known to inhibit cortisol clearance (e.g. antifungals such as itraconazole, antiretroviral drugs) on exogenous steroid that may be stopped Patients on repeated doses of exogenous steroids or where there are clinical concerns about AI

Table 4b Patients who should have a steroid emergency injection kit*

Primary adrenal Insufficiency:	All Causes. Addison's disease, congenital adrenal hyperplasia, bilateral adrenalectomy and adrenal haemorrhage
Pituitary/hypothalamic disease:	1. Patients with hypothalamo-pituitary dysfunction known to be steroid dependent 2. Patients with hypothalamo-pituitary advised to take steroids for intercurrent illness

*clinical discretion should be used and steroid emergency injection kit given to other high risk patients as clinically appropriate