
بسم الله الرحمن الرحيم

NICE guideline

NICE National Institute for Health and Care Excellence

Adrenal insufficiency: identification and management

Published: 28 August 2024

Faezeh Naji

Adrenal insufficiency is the **inadequate production of corticosteroid hormones, mineralocorticoids, and androgens by the adrenal glands.**

Adrenal insufficiency may be **primary, secondary or tertiary.**

Some medicines cause adrenal insufficiency, such as **opioids, checkpoint inhibitors** (used increasingly for treating cancer), **and medicines inhibiting cortisol clearance such as antifungals and antiretrovirals**.

Common causes of adrenal crisis in people with adrenal insufficiency are **gastrointestinal illness (23%), other infections (25%), surgery (10%) and physiological stress (9%).**

The mainstay of **adrenal insufficiency management** is **replacement** with **glucocorticoids (and mineralocorticoids in primary adrenal insufficiency).** These medicines are usually given **orally**, to maintain a good quality of life and to prevent adrenal crisis.

An adrenal crisis is a medical emergency and can be fatal.

Treatment for **adrenal crisis** typically includes **prompt and appropriate** administration of **glucocorticoids (hydrocortisone intravenously or intramuscularly)** and adequate **intravenous fluid hydration with crystalloid.**

This guideline aims to improve the management of adrenal insufficiency and the quality of life of people with adrenal insufficiency.

When to suspect adrenal insufficiency

Consider adrenal insufficiency in people with **unexplained hyperpigmentation**, or when there is **no other clinical explanation for the presence of 1 or more** of the following persistent symptoms, signs or features:

weight loss
salt craving
nausea or vomiting
lack of appetite or unable to eat a full meal
diarrhoea
dizziness or light-headedness on standing
hyponatraemia
hyperkalaemia
lethargy
early puberty
feeling of muscle weakness
hypoglycaemia (particularly in children)
faltering growth (in children)
hypotensive crisis (particularly in children)
prolonged neonatal jaundice.

Adrenal insufficiency is more common in people who:

-**Have recently stopped using glucocorticoids** by any route of administration after **taking them** for more than **4 weeks if aged 16 and over**, or more **than 3 weeks if under16**

-**Are taking glucocorticoids at physiological equivalent doses or above by any route of administration** and have had an episode **of physiological stress**

-**Are taking opioids, checkpoint inhibitors, adrenal enzyme inhibitors or medicines that affect the production, metabolism or action of cortisol, such as antifungals or antiretrovirals**

-Have coexisting conditions such as:

- **primary hypothyroidism**
- **type 1 diabetes**
- **premature ovarian insufficiency**
- **autoimmune polyendocrinopathy syndrome**
- **hypothalamic or pituitary tumours**
- **hypothalamo-pituitary disease including infections and infiltrative disorders**

-Have had **cranial, pituitary, hypothalamic or nasopharyngeal radiotherapy**.

Think about the possibility of adrenal insufficiency in **babies and children** with **differences in sex development**, such **as ambiguous genitalia or bilateral undescended testes.**

Initial investigations for adrenal insufficiency

Do not test for adrenal insufficiency in **people taking oral glucocorticoids at physiological equivalent doses or above.**

Be aware that **people taking exogenous glucocorticoids**, by routes other than oral such **as inhaled, intramuscular or topical, at physiological equivalent doses or above** may have a **low 8 am to 9 am cortisol level.**

Offer an **8 am to 9 am serum cortisol test** to people **aged 1 year and over** with suspected adrenal insufficiency.

Table 1 Interpretation of serum cortisol levels from an 8 am to 9 am test

Serum cortisol level	People aged 16 years and over	Children and young people between 1 year and over, and under 16 years
Below 150 nmol/L	• Recognise that the person may have adrenal insufficiency. • Refer the person to endocrinology. • Consider starting management for adrenal insufficiency (see the section on routine pharmacological management). • If the person is acutely unwell, follow recommendations for people aged 16 and over in the section on emergency management of adrenal crisis.	• Recognise that the person may have adrenal insufficiency. • Refer the person urgently to paediatrics or paediatric endocrinology. • If the person is acutely unwell, follow recommendations for babies, children, and young people under 16 years in the section on emergency management of adrenal crisis.

150 nmol/L to 300 nmol/L	• Recognise that the probability of adrenal insufficiency is uncertain. • Consider repeating the serum cortisol test. • If it remains at this level, seek endocrinology advice or referral.	• Recognise that the probability of adrenal insufficiency is uncertain. • Consider repeating the serum cortisol test. • If it remains at this level, seek paediatric or paediatric endocrinology advice or referral.
Above 300 nmol/L	Recognise that adrenal insufficiency is very unlikely.	Recognise that adrenal insufficiency is very unlikely.

-For babies **under 1 year**, **measure serum cortisol levels at any time** of day and seek paediatric or paediatric endocrinology advice for interpretation of results.

-After an **intramuscular or intra-articular glucocorticoid injection**, **wait 4 weeks** before doing an 8 am to 9 am serum cortisol test.

-Advise people taking **oral oestrogen** to stop taking it for **6 weeks** before serum cortisol is measured because cortisol levels will be falsely elevated **and**:

advise them to use other contraception methods to avoid unplanned pregnancy if oestrogen is used for contraception

If an **adrenal crisis is suspected in a person taking oral oestrogens**, **measure cortisol** but take oral oestrogens into account when **interpreting serum cortisol results.**

Routine pharmacological management

Corticosteroid replacement

Offer **glucocorticoids and mineralocorticoid** (if needed) for people with **primary adrenal insufficiency or congenital adrenal hyperplasia.**

Offer glucocorticoids alone **for people with secondary and tertiary adrenal insufficiency.**

Physiological equivalent doses

The physiological equivalent dose is the dose of glucocorticoid that is equivalent to the amount that a healthy adrenal gland would normally produce:

For people aged 16 years and over this is a **total daily dose of hydrocortisone 15 mg to 25 mg,**
prednisolone 3 mg to 5 mg,
dexamethasone 0.5 mg.

For babies, children and young people under 16 years, this is a total daily dose of **hydrocortisone 8 mg/m2.**

Table 2 Corticosteroid replacement for adrenal insufficiency in people aged 16 years and over

Treatment	Primary adrenal insufficiency	Congenital adrenal hyperplasia (CAH)	Secondary and tertiary adrenal insufficiency
First-choice glucocorticoid	**Hydrocortisone** total daily dose 15 mg to 25 mg orally in 2 to 4 divided doses.	**Hydrocortisone** total daily dose 15 mg to 25 mg orally in 2 to 4 divided doses. Consider higher doses with specialist advice if needed for control of CAH.	**Hydrocortisone** total daily dose 15 mg to 25 mg orally in 2 to 3 divided doses.
Alternative glucocorticoid (for example, if multiple daily doses are not appropriate)	**Prednisolone** (if they have stopped growing) total daily dose 3 mg to 5 mg orally.	**Prednisolone** (if they have stopped growing) total daily dose 3 mg to 5 mg orally. Consider higher doses with specialist advice if needed for control of CAH.	**Prednisolone** (if they have stopped growing) total daily dose 3 mg to 5 mg orally.

Treatment	Primary adrenal insufficiency	Congenital adrenal hyperplasia (CAH)	Secondary and tertiary adrenal insufficiency
Alternative glucocorticoid (for example, if multiple daily doses are not appropriate)	**Modified-release hydrocortisone tablets** (if they have stopped growing) orally. In August 2024, modified-release hydrocortisone tablets were off-label for under 18s. See NICE's information on prescribing medicines.	**Modified-release hydrocortisonecapsules** (if they have stopped growing) orally. Or **dexamethasone** (under specialist advice only) total daily dose 300 micrograms to 500 micrograms orally.	**Modified-release hydrocortisone tablets** (if they have stopped growing) orally. In August 2024, modified-release hydrocortisone tablets were off-label for under 18s. See NICE's information on prescribing medicines.

Mineralocorticoid if needed (to normalise serum electrolytes and plasma renin, and reduce postural symptoms and salt craving)	**Fludrocortisone** total daily dose initially 50 micrograms and adjusted according to response up to 300 micrograms orally. Consider a higher daily dose orally for young and physically active people. In August 2024, doses of fludrocortisone above 300 micrograms daily were off-label. See NICE's information on prescribing medicines.	**Fludrocortisone** total daily dose initially 50 micrograms and adjusted according to response up to 300 micrograms orally. Consider a higher daily dose orally for young and physically active people. In August 2024, doses of fludrocortisone above 300 micrograms daily were off-label. See NICE's information on prescribing medicines.	Do not offer a mineralocorticoid.

Table 3 Corticosteroid replacement for adrenal insufficiency in children and young people between 1 year and over, and under 16 years

Treatment	Primary adrenal insufficiency	Congenital adrenal hyperplasia	Secondary and tertiary adrenal insufficiency
First-choice glucocorticoid	**Hydrocortisone** total daily dose 8 mg/m^2 to 10 mg/m^2 orally in 3 to 4 divided doses.	**Hydrocortisone** total daily dose 9 mg/m^2 to 15 mg/m^2 orally in 3 to 4 divided doses.	**Hydrocortisone** total daily dose 8 mg/m^2 to 10 mg/m^2 orally in 3 to 4 divided doses.
Alternative glucocorticoid (for example, if multiple daily doses are not appropriate)	**Prednisolone** (if they have stopped growing) total daily dose 3 mg to 5 mg orally in 1 to 2 divided doses.	**Prednisolone** (if they have stopped growing) total daily dose 3 mg to 5 mg orally in 1 to 2 divided doses.	**Prednisolone** (if they have stopped growing) total daily dose 3 mg to 5 mg orally in 1 to 2 divided doses.

Alternative glucocorticoid (for example, if there are concerns with adherence or if immediate-release hydrocortisone or prednisolone are unsuitable)	For young people over 12 years, consider **modified-release hydrocortisone tablets** (if they have stopped growing) orally. In August 2024, modified-release hydrocortisone tablets were off-label for under 18s. See NICE's information on prescribing medicines.	For young people over 12 years, consider **modified-release hydrocortisone capsules** (if they have stopped growing) orally.	For young people over 12 years, consider **modified-release hydrocortisone tablets** (if they have stopped growing) orally. In August 2024, modified-release hydrocortisone tablets were off-label for under 18s. See NICE's information on prescribing medicines.

Treatment	Primary adrenal insufficiency	Congenital adrenal hyperplasia	Secondary and tertiary adrenal insufficiency
Mineralocorticoid if needed (to normalise serum electrolytes and plasma renin, and reduce postural symptoms and salt craving)	**Fludrocortisone** total daily dose initially 50 micrograms to 300 micrograms orally, adjusted according to response.	**Fludrocortisone** total daily dose initially 50 micrograms to 300 micrograms orally, adjusted according to response.	Do not offer a mineralocorticoid.

Increase the dose of replacement glucocorticoids in people who are **taking enzyme-inducing medicines** (for example, **antiretroviral medication**).

Do not offer hydrocortisone by **subcutaneous pump or intramuscular or intravenous administration** for routine **daily replacement.**

Hyponatraemia

For people with primary adrenal insufficiency and **persistent hyponatraemia despite** having the **maximum dose of fludrocortisone**, consider **sodium chloride supplementation** according to specialist endocrinology advice.

For people with primary adrenal insufficiency and **severe salt wasting** at presentation (for example, in **newborn babies**), **give 0.9% sodium chloride intravenously** according to specialist endocrinology advice.

Emergency management kits

Give people with primary and secondary adrenal insufficiency 2 or 3 emergency management kits.

Each emergency kit should contain:

- **an intramuscular hydrocortisone injection**
  — premixed hydrocortisone sodium phosphate 100 mg/1 ml (1 vial), or
  — hydrocortisone sodium succinate 100 mg powder and 1 ml water for injection (from a 5- or 10-ml vial)
- **two blue needles**
- **two 2 ml syringes**
- **steroid emergency cards**
- **one orange needle and a 1 ml syringe** (only for babies under 1 year).

Pharmacological management

People aged 16 and over

During periods of **significant physiological stress**, offer at least **40 mg oral hydrocortisone daily in 2 to 4 divided doses** or at least **10 mg oral prednisolone** daily in 1 to 2 divided doses **until the acute illness or physical trauma has resolved.**

Advise **people taking a daily oral prednisolone dose of 10 mg or more** that they **do not need additional sick-day dosing**, but they can **split their total daily dose into 2 equal doses.**

Do not increase glucocorticoid dosing for a long duration.

If the person **vomits within 30 minutes of taking an oral dose**, advise them to **take a further dose once vomiting subsides**, **at double the original dose**.

If **vomiting recurs within 30 minutes**, **give intramuscular hydrocortisone**, and advise the person to attend the emergency department.

Admit the person to hospital during periods of **physiological stress** if they are **unable to absorb oral glucocorticoids**, for example, during prolonged **diarrhoea and vomiting**. Give **100 mg intramuscular or intravenous hydrocortisone**.

For people **who have been admitted to hospital unwell with adrenal insufficiency**, use **sick-day dosing with oral glucocorticoids .**

If **severely unwell (for example, with sepsis)** or in the **intensive care unit**, following the initial dose recommended **200 mg intravenous hydrocortisone over 24 hours or 50 mg intramuscular or intravenous hydrocortisone 4 times a day.**

For people having planned or **emergency surgery or invasive medical procedures**, offer **glucocorticoids (intramuscular or intravenous)** in accordance with tables 1 and 2 in Woodcock et al.

Table 1 Recommended doses for intra- and postoperative steroid cover in adults with primary and secondary adrenal insufficiency.

	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}	Hydrocortisone 200 mg.24 h^{-1} by i.v. infusion while nil by mouth or for patients with postoperative vomiting (alternatively, hydrocortisone 50 mg every 6 h by i.m. injection) Resume enteral – double hydrocortisone doses for 48 h or for up to a week following major surgery. With rapid recovery Resume enteral – double hydrocortisone doses for 24 h
Bowel procedures requiring laxatives/enema.	Bowel prep under clinical supervision. Consider i.v. fluids and injected glucocorticoid 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 24 h
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} Alternatively, hydrocortisone 100 mg intramuscularly followed by 50 mg every 6 h intramuscularly	Resume enteral – double hydrocortisone doses for 48 h
Caesarean section	See surgery under anaesthesia	

i.m., intramuscular; i.v., intravenous.

Table 2. Recommended doses for intra- and postoperative steroid cover in adults receiving adrenosuppresive doses of steroids (prednisolone equivalent ≥ 5 mg 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.24 h^{-1}; Alternatively, dexamethasone 6–8 mg intravenously, if used, will suffice for 24 h	Hydrocortisone 200 mg.24 h^{-1} by i.v. infusion while nil by mouth (alternatively, hydrocortisone 50 mg every 6 h by i.m. injection) Resume enteral glucocorticoid at double the pre-surgical therapeutic dose for 48 h if recovery is uncomplicated. Otherwise continue double oral dose for up to a week
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} Alternatively, dexamethasone 6–8 mg intravenously, if used, will suffice for 24 h	Double regular glucocorticoid dose for 48 h, then continue usual treatment dose if uncomplicated
Bowel procedures requiring laxatives/ enema	Continue normal glucocorticoid dose. Equivalent i.v. dose if prolonged nil by mouth Treat as per primary adrenal insufficiency if concerned about hypothalamo-pituitary-adrenal 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} Alternatively, hydrocortisone 100 mg intramuscularly followed by 50 mg every 6 h intramuscularly	
Caesarean section	See major surgery	

i.m., intramuscular; i.v., intravenous.

[Correction added on 25 June 2020, after first online publication: In Table 2 under Major surgery (Postoperative steroid replacement), the text has been corrected in this current version]

Table 3 Recommended doses for intra- and postoperative steroid cover in children with adrenal insufficiency.

Children	Intra-operative steroid replacement	Postoperative steroid replacement
Major surgery under anaesthesia (general or regional)	Hydrocortisone 2 $mg.kg^{-1}$ at induction followed by immediate continuous i.v. infusion based on weight: Up to 10 kg; 25 $mg.24\ h^{-1}$ 11–20 kg; 50 $mg.24\ h^{-1}$ over 20 kg; - prepubertal 100 $mg.24\ h^{-1}$ - pubertal 150 $mg.24\ h^{-1}$	Hydrocortisone 2 $mg.kg^{-1}$ four hourly intravenously or intramuscularly Or continuous i.v. infusion based on weight: Up to 10 kg; 25 $mg.24\ h^{-1}$ 11–20 kg; 50 $mg.24\ h^{-1}$ over 20 kg; - prepubertal 100 $mg.24\ h^{-1}$ - pubertal 150 $mg.24\ h^{-1}$. Once stable, should receive double usual oral doses of hydrocortisone for 48 h and then reduce to normal doses over up to a week. Add in fludrocortisone if appropriate when enteral feeding established
Minor procedures requiring general anaesthesia	Hydrocortisone 2 $mg.kg^{-1}$ intravenously or intramuscularly at induction of anaesthesia	Double normal hydrocortisone doses once enteral feeding established, and continue on double doses for 24 h. Add in fludrocortisone if appropriate when enteral feeding is established
Minor procedure NOT requiring general anaesthesia	Double morning dose of hydrocortisone given pre-operatively	Normal dose of hydrocortisone

i.v., intravenous.

Pregnancy care

Pre-pregnancy counselling

Provide **pre-pregnancy counselling by clinicians experienced in managing adrenal insufficiency** in pregnancy for anyone with adrenal insufficiency planning a pregnancy.

Emphasise the safety and importance of continuing glucocorticoid (and mineralocorticoid for primary adrenal insufficiency) replacement in pregnancy.

Antenatal care

Monitoring during pregnancy should be done by a multidisciplinary team experienced in managing adrenal insufficiency during pregnancy.

Consider **increasing glucocorticoid (and mineralocorticoid for primary adrenal insufficiency) replacement doses** in the **third trimester** of pregnancy, if needed, **depending on clinical symptoms, sodium levels and postural blood pressure.**

Advise anyone with adrenal insufficiency who is pregnant about the **need to increase doses of hydrocortisone or prednisolone during times of significant psychological or physiological stress:**

For **fever, infection and physical trauma** needing medical attention and **short-term vomiting** related to **illness or early pregnancy**:

Advise the person to **immediately take an additional 20 mg hydrocortisone dose**, **and**

follow sick-day dosing in recommendations 1.4.2 and 1.4.3

•

For **pregnancy-related vomiting**, advise the person to **take glucocorticoids when not feeling nauseated** and to **seek advice from the multidisciplinary team if prolonged.**

For **hyperemesis gravidarum**:

Provide advice to immediately inject **100 mg hydrocortisone intramuscularly** and **go to the emergency department** or early pregnancy unit.

Manage hyperemesis gravidarum in an inpatient setting rather than an outpatient setting. **At the hospital**, **give antiemetics and hydration**.

For people who have been **admitted to hospital** with **hyperemesis gravidarum, give 200 mg intravenous hydrocortisone over 24 hours** or **50 mg intramuscular or intravenous hydrocortisone 4 times a day**.

Intrapartum care

For advice on corticosteroid replacement **during labour ,** follow the recommendations on steroid replacement regimens in NICE's guideline:

For women planning a **vaginal birth** **who have** **adrenal insufficiency or who are taking long-term oral steroids (equivalent to 5 mg or more prednisolone daily for more than 3 weeks):**

- **continue their regular oral steroids** and
- when they are in established **first stage of labour**, add **intravenous or intramuscular hydrocortisone** and consider a minimum dose of **50 mg every 6 hours until 6 hours after the baby is born.**

For women having a planned or emergency **caesarean section** **who have adrenal insufficiency or who are taking long-term oral steroids (equivalent to 5 mg or more prednisolone daily for more than 3 weeks):**

- **continue their regular oral steroids** and
- give **intravenous hydrocortisone** when **starting anaesthesia**; the dose will **depend on whether the woman has received hydrocortisone in labour, for example:**

— consider giving **50 mg if she has had hydrocortisone in labour**
— consider giving **100 mg if she has not had hydrocortisone in labour**

give a further dose of hydrocortisone 6 hours after the baby is born (for example, **50 mg intravenously or intramuscularly**).

Do not offer supplemental hydrocortisone in the intrapartum period to women taking inhaled or topical steroids.

Postpartum care

After the birth, use **sick-day dosing of oral glucocorticoids** for **48 hours** and then resume the usual dose.

If **replacement glucocorticoid (and mineralocorticoid for primary adrenal insufficiency) doses were increased in the third trimester, gradually decrease to pre-pregnancy doses.**

Management during psychological stress

Consider **sick-day dosing** (see recommendation 1.4.2) at times of **severe mental health crisis (for example, a psychotic episode).**

Consider giving **100 mg of intramuscular hydrocortisone** for a person in severe mental health crisis **who is unable to take oral glucocorticoids**

When to suspect adrenal crisis

Consider **adrenal crisis as a potentially reversible cause** in people who are **critically unwell with any of the following:**

low blood pressure (including postural hypotension)

hyperpigmentation (primary adrenal insufficiency only)

hyponatraemia

hypoglycaemia (particularly in children)

circulatory shock or collapse

condition failing to respond to initial treatments.

Emergency management of adrenal crisis:

People aged 16 and over

Give **intravenous or intramuscular hydrocortisone** for suspected adrenal crisis immediately, **being aware that**:

the **intramuscular dose can be given by anyone**, including being self-administered using an emergency management kit

Give **1 litre of 0.9% sodium chloride intravenous infusion over 30 minutes** to the person having an adrenal crisis.

Ensure frequent **monitoring of blood pressure, heart rate, electrolyte, and glucose** status during adrenal crisis.

Continue to give **hydrocortisone** by i**ntravenous infusion** over 24 hours (with monitoring to ensure no interruption of the infusion), or **intramuscular or intravenous injections** (4 times a day) **until the person is haemodynamically stable** and they are **able to take and absorb oral glucocorticoids**.

Continue to give 0.9% sodium chloride intravenous infusion, determined by haemodynamic parameters and electrolyte status, **until the person is haemodynamically stable.**

Offer at least **40 mg oral hydrocortisone daily** in 2 to 4 divided doses or at least **10 mg oral prednisolone** daily in 1 to 2 divided doses **until any underlying cause has resolved and the person is clinically stable.**

Babies, children, and young people under 16 years

For the emergency management of adrenal crisis in babies, children, and young people under 16 years, follow section 1 in the British Society of Paediatric Endocrinology and Diabetes (BSPED) consensus guidelines on adrenal insufficiency.

Emergency Management of Paediatric Adrenal Crisis In the COMMUNITY

Intramuscular (IM) hydrocortisone doses or initial IV dose

Age	IM hydrocortisone Dose	Indications
Less than 1 year	25mg	• Acutely unwell and unable to get IV access • Acutely unwell with diarrhoea and vomiting and unable to tolerate oral treatment • Reduced responsiveness or loss of consciousness. • Hypoglycaemic or new onset seizure in known or suspected adrenal insufficiency. • Fracture / significant burn
1 to 5 years	50mg	
6 years and over	100mg	

Emergency Management of Paediatric Adrenal Crisis in HOSPITAL	
Children (>28 days)*	**Hydrocortisone dose and frequency**
Severe illness	1. Age based doses given IM or IV (25mg < 1year, 50mg 1 to 5 years, 100mg for 6 years and over - subsequent doses as in 2 below) *or* 2. 2mg/kg (max 100mg) IV bolus initially then bolus dose 6 hourly (*can consider giving 4 hourly or as an infusion (see "Major Surgery")
Stable and improving	1mg/kg (max 50mg) IV 6 hourly (can consider giving 4 hourly or as an infusion (see "Major surgery")
Stable and tolerating drinks / diet	Oral sick day steroids: 30mg/m2/day in 4 equally divided doses Restart fludrocortisone if indicated
Neonates (<28 days)	**Hydrocortisone dose and frequency**
Severe illness	4mg/kg IV initially 6 hourly (*can consider giving 4 hourly or as an infusion (see "Major surgery")
Stable and improving	2mg/kg IV 6 hourly (can consider giving 4 hourly or as an infusion (see "Major surgery")
Stable and tolerating drinks / diet	Oral sick day steroids: 30mg/m2/day in 4 equally divided doses Restart fludrocortisone if indicated

** Consider using neonatal doses if small or failing to thrive*

Ongoing care and monitoring
Frequency of reviews

Offer more frequent reviews:

around the time of diagnosis

during periods of rapid growth (including for babies and children, and for young people during puberty)

during periods of rapidly changing family or personal circumstances (such as changes in parental responsibility or moving schools)

during transition of care to adult services

if there are concerns about medicines adherence

During a review ask about:

the **person's psychological wellbeing and ability to carry out everyday activities**

how well they **feel they understand their condition** and **how confident they** are about **managing it medication adherence**

how frequently **they are using additional glucocorticoids (for sick-day dosing and emergency injections)**

their **understanding of sick-day** rules and any education or information needed

the **frequency of adrenal crisis, hospital admissions and infections.**

For babies, children and young people under 16 years with adrenal insufficiency, check:

any changes regarding personal or family circumstances (including education and training)

signs and symptoms of low blood glucose

height and weight

progression to and through puberty and frequency of menstrual periods, if relevant

bone age in children and young people who are still **growing with an X-ray of the left hand and wrist**

bone density (once they have **stopped growing** or if they have had **frequent, low-impact or unexpected fractures).**

Do not routinely carry out cortisol day series to check hydrocortisone dosing

Signs and symptoms of glucocorticoid under-replacement

weight loss

early satiety

decreased appetite

nausea

fatigue that is significantly affecting the person's ability to carry out activities of daily living

worsening hyperpigmentation (in primary adrenal insufficiency)

muscle weakness.

Additional signs and symptoms to monitor in children and young people include **abnormal growth rate and timing of puberty.**

Signs and symptoms of glucocorticoid over-replacement
(for people who are on a higher dose than standard replacement)

weight gain

increased appetite

disturbed sleep

skin thinning

new or worsening diabetes

new or worsening hypertension

Cushingoid appearance

skin infections

acne

thrush

frequent, low-impact or fragility fractures

height loss.

Offer the following measurements and tests to people with adrenal insufficiency and use the results to aid decision making:

blood pressure (lying and standing)

electrolytes

HbA1c

bone density (for adults at least once in the 5 years after diagnosis)

lipid profile (for adults).

Managing glucocorticoid withdrawal to prevent adrenal insufficiency

Glucocorticoid dose-tapering regimens

For people who have been taking glucocorticoids to treat an underlying condition for more than 4 weeks if aged 16 and over (or **more than 3 weeks if under 16 years**) and no longer need them:

reduce glucocorticoids to a daily physiological equivalent dose, and

consider reducing further by using that dose:

every other day for 2 weeks

then twice a week for 2 weeks

then stopping.

For people who have been taking **glucocorticoids for more than 12 weeks** and **no longer need them**, **after reducing to a daily physiological equivalent dose**, consider **stopping treatment using a slower dose-tapering regimen**.

Imperial Centre *for* Endocrinology

I really want to get my prednisolone dose below 3mg, how do I do this?

The other way to reduce prednisolone below 3mg is to take 3mg on some days and 2mg on others. If you take 2mg for one day and 3mg for 6 days, and then slowly increase the number of days that you take 2mg for. It will in fact take 7 weeks to go from 3mg to 2mg. This should slowly help your adrenal gland to recover.

Week	Mon	Tues	Wed	Thurs	Fri	Sat	Sun
0	3	3	3	3	3	3	3
1	3	3	3	2	3	3	3
2	3	2	3	3	2	3	3
3	3	2	3	2	3	2	3
4	2	3	2	3	2	3	2
5	2	3	2	2	3	2	2
6	2	2	2	3	2	2	2
7	2	2	2	2	2	2	2

Do not routinely change from prednisolone to hydrocortisone in people **aged 16 or over** to manage **dose tapering below a physiological equivalent dose**.

Changing to hydrocortisone may be considered in babies, children and young people under 16 years.

Consider **changing from dexamethasone to prednisolone** to **manage dose tapering below a physiological equivalent dose in people aged 16 and over** and **changing to hydrocortisone in babies, children and young people under 16 years.**

For babies, children and young people under 16 years, hydrocortisone may be considered instead. This is because of **dexamethasone being significantly more potent and having a longer half-life,** so it is **difficult to give a corticosteroid-free period over 24 hours, which is not enough for the hypothalamic-pituitary-adrenal axis to recover.**

The committee **highlighted to consider investigations** to **exclude adrenal insufficiency only when a slow tapering regimen has been attempted and the person has developed signs and symptoms of adrenal insufficiency.**

In people who develop **signs and symptoms of adrenal insufficiency** on **glucocorticoid doses below a physiological equivalent dose**, **or in people aged under 16 who have had a low 8 am to 9 am cortisol serum test result after initial glucocorticoid dose tapering** :

prescribe **double the physiological equivalent glucocorticoid dose daily until symptoms resolve.**

then reduce to a daily physiological equivalent dose for 1 week

then stop treatment using a slower tapering regimen as outlined in recommendation 1.9.2 if this has not already been tried.

When and how to test for adrenal insufficiency during glucocorticoid withdrawal

In people aged 16 and over, consider **an 8 am to 9 am serum cortisol** test for adrenal insufficiency **only when a slower dose-tapering regimen has been used** and the **person has developed signs and symptoms of suspected adrenal insufficiency.**

In people aged under 16, consider an **8 am to 9 am cortisol serum** test **following initial glucocorticoid dose tapering even in the absence of signs and symptoms of adrenal insufficiency.**

When doing an 8 am to 9 am serum cortisol test, **pause prednisolone for 24** hours, **hydrocortisone for 12** hours or **dexamethasone for 72** hours before the test**, then restart glucocorticoids at the physiological equivalent dose**.

Table 5 Interpretation of serum cortisol levels from an 8 am to 9 am test during glucocorticoid withdrawal

Serum cortisol level	People aged 16 years and over	Children and young people between 1 year and over, and under 16 years
Below 150 nmol/L	• Restart glucocorticoids. • See the section on routine pharmacological management. • Refer the person to endocrinology.	• Restart glucocorticoids. • See the section on routine pharmacological management. • Refer the person to paediatrics or paediatric endocrinology.
150 nmol/L to 300 nmol/L	• Consider repeating the serum cortisol test. • If it remains at this level, seek endocrinology advice or referral.	• Consider repeating the serum cortisol test. • If it remains at this level, seek paediatric or paediatric endocrinology advice or referral.
Above 300 nmol/L	• Recognise that adrenal insufficiency is very unlikely. • Stop glucocorticoids.	• Recognise that adrenal insufficiency is very unlikely. • Stop glucocorticoids.

Recommendations

The committee recommended that people **aged 1 year and over** with **suspected adrenal insufficiency** should be offered an **8 am to 9 am serum cortisol** test because this is the **optimal time** for peak cortisol levels, and cortisol tests at other random times should not be done.

No reliable evidence was found to support other time frames to accommodate people who work shift patterns, such as night shifts for whom an 8 am to 9 am cortisol test would be **difficult.**

The **circadian clock shifts 1 hour in 24 hours** and so **timings may depend on how many nights have been worked**. A healthcare professional **would avoid testing straight after a night shift** and **wait a few days or consider a different diagnostic test, such as a short synacthen test.**

Due to the variation in diurnal rhythm, **for babies under 1 year**, **serum cortisol levels can be measured at any time of day**.

Studies examining **salivary cortisol** were more recent than those for serum cortisol and used newer assays with **greater accuracy**.

The committee agreed that the use of **salivary cortisol** and **cortisone instead of serum cortisol for first-line testing** is an emerging field.

Potential benefits would be people **being able to do the test themselves at home** and without the need for blood tests, but they agreed that further research is needed.

Corticosteroid replacement

The committee concluded that **dexamethasone** is rarely used in current practice and should only be **considered for people over 16 with CAH if hydrocortisone and prednisolone are unsuitable.** This is because of dexamethasone having a **higher risk of side effects.**

The committee **did not recommend prednisolone for people who are still growing** because of **its effects on growth** but agreed that it may be used for people **who have stopped growing and are having difficulty taking hydrocortisone multiple times a day.**

Prednisolone at doses higher than physiological equivalent doses (**median 7.5** mg a day) has been associated with **poorer health status, with an increased incidence of obesity, hypertension, osteoporosis, and reduced fertility in CAH.**

There is also data for prednisolone showing that **4 mg a day results in physiological replacement serum levels**.

Therefore, **to balance the risk of higher doses causing side effects against inadequate cortisol replacement at lower doses,** endocrinologists prescribe prednisolone doses of **3 mg to 5 mg** as the **starting dose for physiological replacement**

Adherence to glucocorticoid therapy with hydrocortisone tablets can be difficult for people with adrenal insufficiency, because of the need to take **multiple daily doses**.

The committee noted that **younger people in particular can forget or choose to skip doses**. For this reason, they recommended as alternatives either **prednisolone** once or twice a day or **modified-release hydrocortisone** tablets or capsules if there is poor adherence.

Hyponatraemia

For primary adrenal insufficiency, the committee recommended **mineralocorticoid replacement** with **fludrocortisone** to reduce symptoms of hyponatraemia.

They recognised that **physically active and young people** may **need larger doses** **because of salt wasting through sweating and relative resistance to aldosterone.**

Relative resistance to aldosterone is also seen in **young children**, so there is a **need for higher relative doses per body surface** area **in young children too.**

The committee recommended further **supplementation with sodium chloride** in cases where **hyponatraemia persists** **despite having the maximum dose of fludrocortisone**.

The committee noted that **people with tertiary adrenal insufficiency** are **less likely to experience an adrenal crisis.**

This is **because they still have some residual function of the hypothalamic-pituitary-adrenal axis.**

Therefore, they made a weaker recommendation for providing an emergency kit only to those who have a history of adrenal crisis.

A weaker consider recommendation was also made for those **under 16 years old with tertiary adrenal insufficiency** who may be at **more risk of adrenal crisis because of their underlying pathology and stage of physical development**.

A steroid treatment card (blue card) is provided to **people prescribed glucocorticoids for other medical conditions.**

The **card includes guidance** on **minimising the risks when taking corticosteroids and provides details of the prescriber, drug, dosage and duration of treatment.**

Education on **daily dosing, sick-day rules and crisis management** is provided at the time of diagnosis and throughout a person's treatment.

Pregnancy care

Normal pregnancy is associated with **increases in cortisol and aldosterone** that combat the **anti-glucocorticoid and anti-mineralocorticoid effects of progesterone**.

Therefore, **continuing replacement doses of glucocorticoid and mineralocorticoid is essential in pregnancy to prevent adrenal crisis.**

Despite these **increases in cortisol and aldosterone**, which are more apparent by the **third trimester, few people with adrenal insufficiency routinely require increases in their replacement corticosteroid doses.**

Clinical signs including **symptoms of adrenal insufficiency, postural hypotension and hyponatraemia** justify **increases in replacement doses during the third trimester**.

Increased doses of hydrocortisone such as stress doses or injections **will not harm the baby because hydrocortisone is broken down and inactivated in the placenta.**

Many people will experience **nausea and vomiting in pregnancy** and may **not be able to keep their medications down**.

Advice on **taking glucocorticoids during periods of pregnancy-related vomiting** should be provided.

Hyperemesis gravidarum should be **managed within a hospital** setting because **parenteral replacement of increased doses**, **intravenous fluid replacement** and closer **monitoring of blood pressure and serum electrolytes** are often required and are more suited to an inpatient setting.

Glucocorticoid requirements decline after the birth and **if replacement doses have been increased in pregnancy**, they should be **decreased to pre-pregnancy levels** providing there are no complications which may require continuation of increased dosing.

Pharmacological management during psychological stress

This is partly because of the wide variation in factors and events that could lead to **psychological stress**, such as a **mental health crisis or bereavement**, and the variation in what people find stressful and how they react.

Periods of psychological stress could also **vary** between **a short-term or single event to many weeks.** This variation makes it **difficult to determine** whether a person would be **at risk of adrenal crisis** because of psychological stress.

The committee agreed that an **occasional increase in glucocorticoid dose was unlikely to lead to side effects, but longterm increases were not advised.**

Overall, the committee agreed that **a short-term increase in oral glucocorticoids using sick-day dosing for 1 or 2 days could be considered in times of acute and intense psychological or emotional stress.**

For people experiencing a **severe mental health crisis and who cannot take oral glucocorticoids**, the committee advised they should be given **intramuscular hydrocortisone.**

When to suspect adrenal crisis

Evidence available from only **1 study** suggested that **lower sodium levels** are associated with an **increased risk of developing adrenal crisis,** and hyponatraemia below **135** mmol/L is **indicative of adrenal insufficiency and an indicator of the possibility of adrenal crisis.**

No relevant studies were identified that investigated **hyperpigmentation, hypoglycaemia, circulatory shock or collapse, or failure of the condition to respond to initial treatments as risk factors or exposures.**

They noted that **hyperpigmentation** was the **most indicative feature in people with primary adrenal insufficiency** and should raise clinicians' **suspicions of an adrenal crisis** even in the absence of any other signs or symptoms.

By raising awareness of the most common risk factors, signs, and symptoms, delayed and missed diagnosis of adrenal crisis could be reduced, which could save lives.

In considering the **balance of benefits and harms of administering a high dose of hydrocortisone** in an emergency, the committee highlighted **that hydrocortisone is a lifesaving replacement therapy in such situations and it has no toxic dose**. Therefore, they made **strong recommendations for immediate administration of hydrocortisone** and an additional consensus recommendation to reassure that there is no risk of an overdose.

The committee made a consensus recommendation to offer **oral glucocorticoids at a higher dose than usual until any underlying cause has resolved** and the person **is haemodynamically stable** because it is important to **ensure that** the **dose** is **adequate for recovery and for preventing a relapse back into a crisis**.

کارت هشدار پزشکی
نارسایی آدرنال
Adrenal Insufficiency Awareness Card

نام بیمار :

تاریخ تولد :

علت نارسایی آدرنال :

داروهای مصرفی :

- هیدروکورتیزون
- پردنیزولون
- دگزامتازون
- فلودروکورتیزون

توصیه می گردد :

- افزایش دوز کورتون مصرفی بیمار به میزان ۲ برابر در صورت تب، عفونت، تروما، استرس جسمی یا روحی.
- تزریق آمپول هیدروکورتیزون ۱۰۰ mg وریدی در صورت افت فشار خون، تهوع و استفراغ شدید، اسهال، کاهش سطح هوشیاری یا بحران آدرنال.

هشدار: این بیمار مبتلا به نارسایی آدرنال است. در شرایط بحرانی جایگزینی فوری کورتیکواستروئید لازم می باشد .


THANKS FOR YOUR ATTENTION