NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Guideline

Adrenal insufficiency: identification and management

Draft for consultation, March 2024

This guideline covers identifying and managing adrenal insufficiency (hypoadrenalism) in babies, children, young people, and adults. It aims to improve the treatment of primary, secondary, and tertiary adrenal insufficiency and also the prevention and management of adrenal crisis.

Who is it for?

- Health and social care practitioners providing NHS-commissioned services, including those working in dental services, school health services and pre-hospital care
- Commissioners of health and social care services
- People with adrenal insufficiency, their families, and carers

What does it include?

- the recommendations
- recommendations for research
- rationale and impact sections that explain why the committee made the recommendations and how they might affect practice
- the guideline context.

Information about how the guideline was developed is on the guideline's webpage. This includes the evidence reviews, the scope, details of the committee and any declarations of interest.

Contents

Recommendations

People have the right to be involved in discussions and make informed decisions about their care, as described in NICE's information on making decisions about your care.

Making decisions using NICE guidelines explains how we use words to show the strength (or certainty) of our recommendations and has information about prescribing medicines (including off-label use), professional guidelines, standards, and laws (including on consent and mental capacity), and safeguarding.

1.1 Information and support

1.1.1 For advice on communicating with and providing information for people with suspected or diagnosed adrenal insufficiency, follow the recommendations in NICE's guidelines on patient experience in adult NHS services and babies, children and young people's experience of healthcare. For advice on shared decision making, follow the recommendations in NICE's guideline on shared decision making.

1.1.2 When making decisions on care with people with adrenal insufficiency and learning disabilities, follow the recommendations in NICE's guideline on decision making and mental capacity.

At diagnosis

1.1.3 Give information to people with adrenal insufficiency and their families and carers on:

- how to obtain an NHS Steroid Emergency Card for adults, British Society of Paediatric Endocrinology and Diabetes (BSPED) Emergency Steroid Card for children and young people, and medical alert jewellery
- how to set up medical alerts, medical IDs, and apps on mobile phones
- relevant support groups and charities for people with adrenal insufficiency
- how to access free NHS prescriptions

- how to discuss their diagnosis and treatment with employers, in educational settings, and with friends and family.

1.1.4 Reassure people that having adrenal insufficiency does not prevent living a full and active life, and give information on the following topics to help them, and their families and carers, make informed decisions to support self-management:

- The importance of glucocorticoid as a life-essential hormone replacement and lifesaving treatment for adrenal crisis.
- Why they have been prescribed glucocorticoids (plus mineralocorticoids for primary adrenal insufficiency) and the planned duration of treatment.
- Long- and short-term side effects because of under- or over-hormone replacement and symptoms to look out for.
- When to take additional glucocorticoids, for example at times of physiological or significant psychological stress.
- How to seek clinical advice when unwell, including when to access or call emergency services (for example, using the 999 service).
- How to administer glucocorticoids in an emergency and seek medical advice after using emergency medicine.
- The need to maintain a good supply of oral medicines at all times, including when travelling or moving between places of residence and how to obtain additional supplies if needed for sick-day dosing.
- How to adjust the timing of medicine dosing when travelling through time zones, fasting, or doing shift work or activities that affect sleep patterns.
- The importance of not stopping medicines abruptly except when based on clinical advice.

See also NICE's guidelines on medicines adherence and medicines optimisation.

Providing management plans and information to other settings

1.1.5 Provide a management plan to parents or carers of children and young people with adrenal insufficiency. Advise them to share the plan and discuss their child's needs with the school and any other caregivers.

1.1.6 Advise healthcare providers in other settings (including residential care and prisons) about the needs of the person with adrenal insufficiency and provide a management plan.

See also the NICE guideline on managing medicines in care homes and the section on communication and coordination in the NICE guideline on physical health of people in prison.

Reviewing information and support needs

1.1.7 Review information and support needs regularly as children grow up, during times of transition (for example, starting school or university) and when significant life events occur (for example, when having children). See also NICE's guideline on transition from children's to adult services for young people using health or social care services.

1.1.8 Continue to offer information and support even if this has been declined previously.

Carers

1.1.9 Explain to carers (including young carers) about their right to a carer's assessment and tell them about other sources of information and support (see NICE's guideline on supporting adult carers and the Young Carers [Needs Assessments] Regulations 2015).

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on information and support.

Full details of the evidence and the committee's discussion are in evidence review A: information and support.

1.2 Initial identification and referral

When to suspect adrenal insufficiency

1.2.1 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
- feeling of muscle weakness
- hypoglycaemia (particularly in children)
- faltering growth (in children)
- hypotensive crisis (particularly in children)
- prolonged neonatal jaundice.

1.2.2 When carrying out an initial assessment in a person who presents with any unexplained symptoms, signs or features in recommendation 1.2.1 be aware that 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 under 16 years
- are taking glucocorticoids at physiological equivalent doses by any route of administration and have had an episode of physiological stress

- are taking opioids, checkpoint inhibitors, adrenal enzyme inhibitors or medicines that interfere with 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 type 1
  - hypothalamic and pituitary tumours
  - hypothalamo-pituitary disease including infections and infiltrative disorders
- have had cranial, pituitary, hypothalamic or nasopharyngeal radiotherapy.

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

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on when to suspect adrenal insufficiency.

Full details of the evidence and the committee's discussion are in evidence review B: when to suspect adrenal insufficiency.

Initial investigations for adrenal insufficiency (not including people withdrawing from exogenous glucocorticoids)

1.2.4 Offer an 8 am to 9 am serum cortisol test to people with suspected adrenal insufficiency. Follow table 1 to interpret the results and aid decision making.

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

Serum cortisol level	Action
Below 150 nmol/L	Start management for adrenal insufficiency (see the section on routine pharmacological management) and refer the person to endocrinology
Between 151 and 200 nmol/L	Refer the person to endocrinology or arrange a short synacthen test (and discuss abnormal results with endocrinology)
Between 201 nmol/L and 300 nmol/L	Consider repeating the test and if it remains at this level, refer the person to endocrinology or arrange a short synacthen test
Above 300 nmol/L	Recognise that adrenal insufficiency is very unlikely

1.2.5 Do not do a cortisol test at random times of day to rule out adrenal insufficiency.

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

1.2.7 Advise people taking oral oestrogen to stop taking it for 6 weeks before measuring serum cortisol because cortisol levels will be falsely elevated and:

- consider a switch to a transdermal preparation if used for hormone replacement therapy
- use other contraception methods to avoid unplanned pregnancy if used for contraception.

1.2.8 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.

1.2.9 In people withdrawing from exogenous glucocorticoids below the physiological equivalent dose, see the section on managing glucocorticoid withdrawal to prevent adrenal insufficiency.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on initial investigations.

Full details of the evidence and the committee's discussion are in evidence review D: diagnostic tests and diagnostic thresholds for referral.

1.3 Routine pharmacological management

Steroid replacement

1.3.1 Offer glucocorticoid and mineralocorticoid replacement for people with primary adrenal insufficiency and glucocorticoids only for people with secondary and tertiary adrenal insufficiency.

1.3.2 When prescribing a steroid, follow:

- table 2 for people aged 16 years and over
- table 3 for children and young people over 1 year and under 16 years
- table 4 for babies under 1 year.

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

Treatment	Primary adrenal insufficiency	Secondary and tertiary adrenal insufficiency
First-choice glucocorticoid	**Hydrocortisone** total daily dose 15 mg to 25 mg orally in 2 to 4 divided doses. For CAH, consider higher doses with specialist advice.	**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 in 1 to 2 divided doses. For CAH, consider higher doses with specialist advice.	**Prednisolone** (if they have stopped growing) total daily dose 3 mg to 5 mg orally in 1 to 2 divided doses
Alternative glucocorticoid	Non-CAH (if they have stopped growing): **modified-release hydrocortisone** total daily	**Modified-release hydrocortisone** (if they have stopped growing):

	dose 20 mg to 30 mg orally. CAH (if they have stopped growing): **modified-release hydrocortisone** total daily dose 20 mg to 30 mg orally. **or** **dexamethasone** total daily dose 300 micrograms to 500 micrograms orally.	total daily dose 20 mg to 30 mg orally
Mineralocorticoid (to normalise serum electrolytes and plasma renin, and reduce postural symptoms and salt craving)	**Fludrocortisone** total daily dose 50 micrograms to 300 micrograms orally. Consider a higher daily dose orally for young and physically active people. In January 2023, doses of fludrocortisone above 300 micrograms daily were off-label. See NICE's information on prescribing medicines.	Do not offer a mineralocorticoid.

Table abbreviations: CAH, congenital adrenal hyperplasia.

See the BNF for appropriate use and dosing in specific populations, for example, people with hepatic or renal impairment, in pregnancy and breastfeeding.

For multiple daily doses, give the larger dose in the morning and the smaller in the evening, mimicking the normal diurnal rhythm of cortisol secretion, the optimum daily dose is determined on the basis of clinical response.

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

Treatment	Primary adrenal insufficiency	Secondary and tertiary adrenal insufficiency
First-choice glucocorticoid	Non-CAH: **hydrocortisone** total daily dose 8 mg/m^2 to 10 mg/m^2 orally in 3 to 4 divided doses CAH: **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	If they have stopped growing **prednisolone** total daily dose 3 mg to 5 mg orally in 1 to 2 divided doses.	If they have stopped growing **prednisolone** total daily dose 3 mg to 5 mg orally in 1 to 2 divided doses.
Alternative glucocorticoid	For young people over 12 years, consider **modified-release hydrocortisone** orally 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** orally if there are concerns with adherence or if immediate-release hydrocortisone or prednisolone are unsuitable.
Mineralocorticoid (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.	Do not offer a mineralocorticoid.

1 Table abbreviations: CAH, congenital adrenal hyperplasia.

2 See the BNFC for appropriate use and dosing in specific populations, for example,
3 people with hepatic or renal impairment.

4 For multiple daily doses, give the larger dose in the morning and the smaller in the
5 evening, mimicking the normal diurnal rhythm of cortisol secretion, the optimum daily
6 dose is determined on the basis of clinical response.

Table 4 Steroid replacement for adrenal insufficiency in babies under 1 year

Treatment	Primary adrenal insufficiency	Secondary and tertiary adrenal insufficiency
Glucocorticoid	Non-CAH: **hydrocortisone** total daily dose 8 mg/m^2 to 10 mg/m^2 orally in 3 to 4 equally divided doses. CAH: **hydrocortisone** total daily dose 9 mg/m^2 to 15 mg/m^2 orally in 3 to 4 equally divided doses.	**Hydrocortisone** total daily dose 8 mg/m^2 to 10 mg/m^2 orally in 3 to 4 equally divided doses.
Mineralocorticoid	**Fludrocortisone** total daily dose initially 50 micrograms to 200 micrograms orally. Higher doses once daily may be required, and dose adjustment may be required if salt supplements are given.	Do not offer a mineralocorticoid.

Table abbreviations: CAH, congenital adrenal hyperplasia.

See the BNFC for appropriate use and dosing in specific populations, for example, people with hepatic or renal impairment.

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

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

Hyponatraemia

1.3.5 For people with primary adrenal insufficiency and persistent hyponatraemia despite mineralocorticoid replacement, consider sodium chloride supplementation according to specialist endocrinology advice.

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

Emergency management kits

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

1.3.8 Consider giving people aged 16 and over with tertiary adrenal insufficiency who have a history of adrenal crisis an emergency management kit.

1.3.9 Each emergency kit should contain:

- intramuscular hydrocortisone injection
  - premixed hydrocortisone sodium phosphate 100 mg/1 ml (1 vial), or
  - hydrocortisone sodium succinate 100 mg powder and 5- or 10-ml water for injection (1 vial)
- two blue needles
- two 2 ml syringes
- written instructions in an easy-to-understand format (for example, with diagrams or pictures) on how to prepare and give emergency intramuscular hydrocortisone and how to safely dispose of needles and syringes
- steroid emergency cards
- for babies, children and young people under 16, consider including glucose gel
- for babies under 1 year, think about including 1 orange needle and a 1 ml syringe.

1.3.10 Provide training on how to use emergency management kits. Advise people with adrenal sufficiency and their carers to check the expiry date on hydrocortisone, needles and syringes and replace, as necessary.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on routine pharmacological management.

Full details of the evidence and the committee's discussion are in evidence review F: routine pharmacological management of primary adrenal insufficiency, evidence review G: routine pharmacological management of secondary and tertiary adrenal insufficiency, and evidence review I: emergency management of adrenal insufficiency.

1.4 Management during physiological stress

Pharmacological management

1.4.1 Offer additional supplies of oral glucocorticoids to cover increased dosing during periods of physiological stress (sick-day dosing). For people on modified-release hydrocortisone, provide supplies of immediate-release hydrocortisone. See recommendation 1.1.4 for information and support on sick-day rules.

People aged 16 and over

1.4.2 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.

1.4.3 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.

1.4.4 Be aware of the risks of increased glucocorticoid dosing for a prolonged duration (see signs and symptoms of glucocorticoid over-replacement in box 1).

1.4.5 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.

1.4.6 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. See recommendation 1.7.1 on emergency management of adrenal crisis.

1.4.7 For people who have been admitted to hospital unwell with adrenal insufficiency, use sick-day dosing with oral glucocorticoids (see recommendation 1.4.2). If severely unwell, for example with sepsis, or in the intensive care unit, give 200 mg intravenous hydrocortisone over 24 hours or 50 mg intramuscular or intravenous hydrocortisone 4 times per day. Think about seeking endocrinology specialist advice if needed.

1.4.8 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.

Babies, children and young people up to 16 years

1.4.9 For babies, children and young people up to 16 years follow section 2: major surgery, section 3: minor procedures, section 4: sick day rules and section 5: pre-calculated oral hydrocortisone sick day doses in the British Society of Paediatric Endocrinology and Diabetes (BSPED) consensus guidelines on adrenal insufficiency.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on pharmacological management during physiological stress.

Full details of the evidence and the committee's discussion are in evidence review J: pharmacological management during physiological stress.

Non-pharmacological management

1.4.10 Give people with, or at high risk of, adrenal insufficiency and their family and carers information on daily dosing, sick-day rules and crisis

management during periods of physiological stress. See recommendation 1.1.4 for information and support on managing physiological stress.

1.4.11 Offer blue steroid treatment cards to people on exogenous glucocorticoids for non-endocrine conditions who are at risk of tertiary adrenal insufficiency.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on non-pharmacological management during physiological stress.

Full details of the evidence and the committee's discussion are in evidence review L: non-pharmacological management during physiological stress.

Pregnancy care

Pre-pregnancy counselling

1.4.12 Provide anyone with adrenal insufficiency who is planning to become pregnant with pre-pregnancy counselling from clinicians experienced in managing adrenal insufficiency in pregnancy.

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

Antenatal care

1.4.14 Advise anyone with adrenal insufficiency who is pregnant to tell their GP and pregnancy specialist as soon as possible.

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

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

1.4.17 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 vomiting during pregnancy, advise the person where possible to take glucocorticoids when not feeling nauseated.
- For prolonged pregnancy-related vomiting, seek advice from the multidisciplinary team.
- 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 unwell with hyperemesis gravidarum, give 200 mg intravenous hydrocortisone over 24 hours or 50 mg intramuscular or intravenous hydrocortisone 4 times per day.
  - Seek specialist advice from the obstetric medicine team or endocrinology team about the dosage and duration of high-dose hydrocortisone during the hospital stay.
  - After discharge, follow sick-day dosing in recommendations 1.4.2 and 1.4.3 until daily vomiting stops.

Intrapartum care

1.4.18 For anyone with adrenal insufficiency planning a vaginal birth or having a planned or emergency caesarean section, follow the recommendations in the section on steroid replacement regimens in the NICE guideline on

intrapartum care for women with existing medical conditions or obstetric complications and their babies.

Postpartum care

1.4.19 After the birth of the baby, use sick-day dosing of oral glucocorticoids for 48 hours and then resume the usual dose. For ongoing postpartum physiological stress, follow sick-day dosing in recommendation 1.4.2.

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

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on pregnancy care.

Full details of the evidence and the committee's discussion are in evidence review J: pharmacological management during physiological stress.

1.5 Management during psychological stress

Pharmacological management

People aged 16 years and over

1.5.1 Consider sick-day dosing (see recommendation 1.4.2) for 1 or 2 days during psychological stress.

1.5.2 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.

Babies, children and young people up to 16 years

1.5.3 For babies, children and young people up to 16 years experiencing psychological stress consider sick-day dosing for 1 to 2 days and follow section 5: pre-calculated oral hydrocortisone sick day doses in the British

Society of Paediatric Endocrinology and Diabetes (BSPED) consensus guidelines on adrenal insufficiency.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on pharmacological management during psychological stress.

Full details of the evidence and the committee's discussion are in evidence review K: pharmacological management during psychological stress.

Non-pharmacological management

1.5.4 Advise people with adrenal insufficiency to reduce or manage psychological stress by:

- using condition-specific patient support groups that offer peer support or other organisations offering information and support
- exploring with their employer or education provider any adjustments that could be made in the workplace or educational setting
- exploring the role of self-management (including activities they could take part in to reduce their stress).

1.5.5 Consider referring the person, or ask the person to self-refer, to NHS talking therapies or mental health services, in line with NICE guidelines on managing anxiety and depression.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on non-pharmacological management during psychological stress.

Full details of the evidence and the committee's discussion are in evidence review M: non-pharmacological management during psychological stress.

1.6 When to suspect adrenal crisis

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

- low blood pressure (including postural hypotension)
- hyperpigmentation
- hyponatraemia
- hyperkalaemia
- hypoglycaemia (particularly in children)
- circulatory shock or collapse
- condition failing to respond to initial treatments.

1.6.2 Consider adrenal crisis in people with, or at high risk of, adrenal insufficiency (see recommendation 1.2.1) who are unwell with milder symptoms, including:

- lethargy
- pallor
- clamminess
- feeling cold or feverish
- confusion or altered mental states
- weakness.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on when to suspect adrenal crisis.

Full details of the evidence and the committee's discussion are in evidence review H: when to suspect adrenal crisis.

1.7 Emergency management of adrenal crisis

People aged 16 and over

1.7.1 Give intravenous or intramuscular hydrocortisone for suspected adrenal crisis without delay, being aware that:

- the intramuscular dose can be given by anyone, including being self-administered using an emergency management kit
- there is no risk of overdose from hydrocortisone in an emergency situation.

1.7.2 Advise people having an adrenal crisis to immediately go to hospital in an ambulance and that a GP does not need to liaise with the hospital first.

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

1.7.4 Ensure people having an adrenal crisis receive frequent monitoring of blood pressure, heart rate, electrolyte, and glucose status.

1.7.5 Continue to give hydrocortisone by intravenous infusion over 24 hours, 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.

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

1.7.7 Use sick-day dosing (see recommendation 1.4.2) until any underlying cause has resolved and the person is clinically stable.

1.7.8 Identify and treat any underlying cause of adrenal crisis.

1.7.9 Refer to the specialist endocrine team for ongoing clinical advice and support throughout admission and during the hospital stay.

Babies, children, and young people under 16 years

1.7.10 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.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on emergency management of adrenal crisis.

Full details of the evidence and the committee's discussion are in evidence review I: emergency management of adrenal crisis.

1.8 Ongoing care and monitoring

1.8.1 Offer ongoing reviews with an appropriate specialist team for people with adrenal insufficiency.

1.8.2 Offer children and young people under 16 years an appointment at least every 6 months and a face-to-face review at least annually to measure their height and weight and adjust glucocorticoid dose accordingly.

1.8.3 Adjust the frequency of ongoing reviews according to clinical and individual needs using a shared decision-making model.

1.8.4 Offer more frequent reviews:

- around the time of diagnosis
- during periods of rapidly changing clinical needs
- 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)
- at the time of transition of care to adult services
- if there are concerns about medicines adherence
- if there are concerns about the person, their carers or family being able to safely manage the condition
- for vulnerable people.

1.8.5 Be aware that the following groups are likely to need less frequent reviews:

- adults on exogenous glucocorticoids

- adults who are confident with self-management
- adults with stable clinical needs.

1.8.6 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.

1.8.7 Monitor for signs and symptoms of glucocorticoid under- or over-replacement (see box 1), aiming for physiological glucocorticoid replacement dosing.

Box 1 Signs and symptoms of glucocorticoid under- or over-replacement

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 faltering growth and early 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 or low-impact fractures
- height loss
- fragility fractures.

1.8.8 For primary adrenal insufficiency:

- also monitor for signs and symptoms of mineralocorticoid under-replacement (light-headedness or salt craving) or over-replacement (swollen ankles or high blood pressure)
- consider measuring renin and adjust fludrocortisone dose if needed.

1.8.9 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 every 3 to 5 years)
- lipid profile (for adults).

1.8.10 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, for example, light-headedness
- 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).

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

1.8.12 Advise the person to adjust glucocorticoid dose depending on lifestyle factors and any temporary increased demands on activities of daily living (for example, an unusually long day, endurance exercise, shift working, and travel).

1.8.13 Give guidance and information on transitioning from services for young people taking over responsibility for their own health and care from their parents in line with NICE's guideline on transition from children's to adults' services for young people using health or social care services.

People receiving end of life care: additional considerations

1.8.14 Offer glucocorticoids to people with adrenal insufficiency who are receiving end of life care unless as part of shared decision making it has been decided to withdraw active treatment.

1.8.15 Offer once-daily formulations and routes of administration, for example, subcutaneous or intramuscular.

1.8.16 See NICE's guidelines on end of life care for adults, end of life care for infants, children and young people with life-limiting conditions, and shared decision making for further information.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on ongoing care and monitoring for people with adrenal insufficiency and people with adrenal insufficiency receiving end of life care.

Full details of the evidence and the committee's discussion are in evidence review N: ongoing care and monitoring including end of life care.

1.9 Managing glucocorticoid withdrawal to prevent adrenal insufficiency

Glucocorticoid dose tapering regimens

1.9.1 For people 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 who no longer need them, reduce glucocorticoids to a daily physiological equivalent dose, then consider reducing further by taking that dose:

- every other day for 2 weeks
- then twice a week for 2 weeks
- then stopping.

Decisions to taper dosages of glucocorticoid should be made by the clinical team who initiated the treatment.

1.9.2 For people who have had glucocorticoids for longer than 12 weeks, once a daily physiological equivalent dose is reached, consider stopping treatment using a slower dose tapering regimen than in recommendation 1.9.1. Calculate the weekly cumulative glucocorticoid dose and reduce this by 10% each week, rounding to the nearest practicable dose.

1.9.3 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.

1.9.4 Do not routinely change from prednisolone to hydrocortisone to manage dose tapering below a physiological equivalent dose.

1.9.5 Tell people who are tapering glucocorticoid doses below a physiological equivalent dose:

- to expect temporary symptoms, including fatigue, reduction in appetite and low mood
- about sick-day rules and glucocorticoid cover for invasive procedures and surgery (see recommendation 1.1.4).

1.9.6 Monitor people on glucocorticoid dose tapering below physiological equivalent dose regimens for signs and symptoms of adrenal insufficiency (see section on when to suspect adrenal insufficiency) and provide advice for family and carers about potential symptoms to expect.

1.9.7 In people who develop signs and symptoms of adrenal insufficiency on glucocorticoid doses below a physiological equivalent dose:

- 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

1.9.8 Consider an 8 am to 9 am serum cortisol test for adrenal insufficiency only when a slower dose tapering regimen has been done (as outlined in recommendation 1.9.2) and the person has developed signs and

symptoms of suspected adrenal insufficiency (see section on when to suspect adrenal insufficiency) and:

- Pause prednisolone for 24 hours, or hydrocortisone for 12 hours, or dexamethasone for 72 hours, before the 8 am to 9 am serum cortisol test then restart glucocorticoids at the physiological equivalent dose.
- If the result from the 8 am to 9 am serum cortisol test is above 300 nmol/L adrenal insufficiency is unlikely and glucocorticoids can be withdrawn.
- If the result from the 8 am to 9 am serum cortisol test is below 300 nmol/L consider restarting glucocorticoids and refer the person to endocrinology.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on managing glucocorticoid withdrawal to prevent adrenal insufficiency.

Full details of the evidence and the committee's discussion are in evidence review B: when to suspect adrenal insufficiency, evidence review C: when to refer for steroid withdrawal and evidence review E: methods for corticosteroid withdrawal.

Terms used in this guideline.

This section defines terms that have been used in a particular way for this guideline.

Emergency management kit

An emergency management kit contains hydrocortisone for intramuscular injection that can be given by anyone, including the person with adrenal insufficiency, when adrenal crisis is suspected.

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, prednisolone 3 mg, or dexamethasone 0.5 mg.

- For babies, children and young people under 16 years this is a total daily dose of hydrocortisone 8 mgs/m^2.

Physiological stress

Physiological stress is when a person has a fever, or a physical trauma requiring medical attention and covers intercurrent illness, invasive procedures, surgery, and pregnancy (including labour or pregnancy loss).

Primary adrenal insufficiency

Primary adrenal insufficiency is caused by disease in the adrenal glands themselves (the autoimmune condition Addison's disease is the most common cause in adults, and congenital adrenal hyperplasia is the most common cause in children).

Psychological stress

Periods of sudden, intense psychological and emotional stress such as a bereavement.

Secondary adrenal insufficiency

Secondary adrenal insufficiency is caused by inadequate adrenocorticotropic hormone production by the pituitary gland (often because of treatment for a pituitary disease, or from pituitary tumours and their treatment).

Sick-day dosing

A set of guidelines for adjusting medication dosages during periods of physiological stress. When people are unwell their usual medication regimen may need adjustments to mimic the usual increase in cortisol during physiological stress.

Sick-day rules

Information to help people understand how to adjust medication during periods of physiological stress.

Tertiary adrenal insufficiency

Tertiary adrenal insufficiency is caused by inadequate corticotrophin-releasing hormone production by the hypothalamus (sometimes because of treatment for tumours in the hypothalamus or adjoining structures, or more commonly because of

taking glucocorticoids for more than 4 weeks causing hypothalamic-pituitary-adrenal axis suppression). Stopping glucocorticoids may also cause adrenal insufficiency.

Recommendations for research

The guideline committee has made the following recommendations for research.

Key recommendations for research

1 Initial investigations for people with suspected adrenal insufficiency

What is the clinical and cost effectiveness of salivary cortisone or cortisol to identify people with adrenal insufficiency?

> For a short explanation of why the committee made this recommendation for research, see the rationale and impact section on initial investigations.
>
> Full details of the evidence and the committee's discussion are in evidence review D: diagnostic tests and thresholds for referral.

2 Glucocorticoid withdrawal

In people at risk of adrenal insufficiency because of prolonged glucocorticoid use, what is the best way to manage glucocorticoid withdrawal when they are no longer needed?

> For a short explanation of why the committee made this recommendation for research, see the rationale and impact section on managing glucocorticoid withdrawal to prevent adrenal insufficiency.
>
> Full details of the evidence and the committee's discussion are in evidence review E: methods for corticosteroid withdrawal.

3 Adrenal crisis

What increases the risk of adrenal crisis and adverse hospital outcomes in people taking long-term steroids?

For a short explanation of why the committee made this recommendation for research, see the rationale and impact section on when to suspect adrenal crisis.

Full details of the evidence and the committee's discussion are in evidence review H: when to suspect adrenal crisis.

4 Routine pharmacological management in secondary and tertiary adrenal insufficiency

What is the clinical and cost effectiveness of glucocorticoids for the routine management of secondary and tertiary adrenal insufficiency?

For a short explanation of why the committee made this recommendation for research, see the rationale and impact section on routine pharmacological management.

Full details of the evidence and the committee's discussion are in evidence review G: routine pharmacological management of secondary and tertiary adrenal insufficiency.

5 Pharmacological management of physiological stress

What is the clinical and cost effectiveness of postoperative glucocorticoids for people with, or at risk of, adrenal insufficiency having inpatient invasive procedures?

For a short explanation of why the committee made this recommendation for research, see the rationale and impact section on management during physiological stress.

Full details of the evidence and the committee's discussion are in evidence review J: pharmacological management of physiological stress.

Rationale and impact

These sections briefly explain why the committee made the recommendations and how they might affect practice.

Information and support

Recommendations 1.1.1 to 1.1.9

Why the committee made the recommendations

A qualitative review identified studies investigating information and support needs for adults and children with adrenal insufficiency and their carers. There was some evidence addressing the routine management of adrenal insufficiency and support for preventing adrenal crisis, but overall, the evidence was limited because it did not cover all aspects of information and support needs specified in the review questions. It was graded as medium to low quality mainly because of methodological limitations in the studies.

The main themes from the evidence included improving awareness of physiological stress situations that might require an increased dose of hydrocortisone, the need for more information and education throughout a person's treatment, and the value of patient support groups. These themes support the recommendations on giving additional glucocorticoids, signposting people to support groups and networks for their clinical condition, and reviewing information and support needs regularly, in particular, the needs of children and young people as they mature and transition to adulthood. Studies did not specifically address information and support in emergency care during adrenal crisis, or when fasting, travelling, or working non-standard hours.

Adults are advised on how to get an NHS Steroid Emergency Card, including people who may develop tertiary adrenal insufficiency and become steroid-dependent. This prompts healthcare professionals to consider adrenal crises in people carrying the card, start appropriate management for planned surgery or invasive procedures, and treat people rapidly in emergency situations. Children with adrenal insufficiency should have a BSPED adrenal insufficiency card that provides parents, carers, and healthcare staff with a child's steroid care plan for sick days and emergencies. The committee therefore used their expertise from clinical practice to develop consensus recommendations for these specific areas.

How the recommendations might affect practice

The recommendations are reflective of best practice and are not expected to lead to significant changes.

Return to recommendations

Initial identification and referral

When to suspect adrenal insufficiency

Recommendations 1.2.1 to 1.2.3

Why the committee made the recommendations

Evidence on the diagnostic accuracy of signs and symptoms associated with adrenal insufficiency was limited, but the symptoms and signs reported in studies were generally in line with the committee's clinical experience. Evidence was identified for low blood pressure, hyperpigmentation for primary adrenal insufficiency, lethargy, salt craving, weight loss, hyponatraemia, hyperkalaemia, nausea, vomiting and diarrhoea. The committee agreed more importance should be placed on the sensitivity of a test for clinical decision making, but none of the signs and symptoms met the agreed thresholds for both sensitivity and specificity. The symptoms and signs of adrenal insufficiency are common to many conditions. One or more persistent and unexplained symptoms, signs or features should raise suspicion of adrenal insufficiency and warrant further investigation. The committee agreed hyperpigmentation is common in people with primary adrenal insufficiency and the clearest indicator for the condition. Symptoms and signs particularly seen in children are hypoglycaemia, faltering growth, hypotensive crisis, and differences in sex development.

The committee made consensus recommendations drawing on their experience of observed symptoms and signs, and knowledge of the risk of adrenal insufficiency associated with some medications and coexisting conditions and comorbidities, such as hypothyroidism and type 1 diabetes.

How the recommendations might affect practice

The recommendations generally reflect current best practice and are not expected to lead to significant changes. They may be useful in particular for non-specialist clinicians in acute areas such as pre-hospital emergency care and emergency departments, and for those doing invasive procedures or surgery. Increased awareness of the possibility of adrenal insufficiency may reduce mortality by enabling early diagnosis and treatment.

Return to recommendations

Initial investigations for adrenal insufficiency (not including people withdrawing from exogenous glucocorticoids)

Recommendations 1.2.4 to 1.2.9

There was limited evidence for this review question because of small numbers of study participants and diversity between studies, so the committee used their clinical knowledge and experience to make the recommendations.

The committee recommended that people 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. When interpreting 8 am to 9 am serum cortisol results, it is important to take into account clinical context. People with symptoms of adrenal insufficiency together with hyponatraemia may need discussion with endocrinology, especially if cortisol is between 150 and 200 nmol/L. They may have developed acute adrenal insufficiency related to other treatments such as checkpoint inhibitors.

Because of a ‘grey area’ of clinical suspicion between 200 and 300 nmol/L the committee concluded that if the test result falls between these values a repeat 8 am to 9 am serum cortisol test should be considered. The committee set an upper threshold of 300 nmol/L for re-testing because they agreed that any reading above this would mean adrenal insufficiency is very unlikely.

Serum cortisol tests in people who are taking oral oestrogens are not accurate because cortisol levels are falsely elevated because oestrogen raises levels of

cortisol binding globulin. Therefore, the committee recommended people stop taking it 6 weeks before measuring serum cortisol.

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 and therefore made a recommendation for research.

How the recommendations might affect practice

Serum cortisol testing in current practice is not consistently done at the optimal time to diagnose adrenal insufficiency. Therefore, the recommendations will not affect the total number of tests done but may result in a change in practice for some providers. Optimal serum cortisol testing and the use of the recommended referral threshold should minimise costly and unnecessary referrals to secondary care and short synacthen testing.

Return to recommendations

Routine pharmacological management

Recommendations 1.3.1 to 1.3.10

Steroid replacement

Why the committee made the recommendations

There was insufficient evidence for the committee to support a change from the current clinical practice of using hydrocortisone for glucocorticoid replacement as routine first-choice treatment for adrenal insufficiency. Limited evidence was found comparing different doses of oral hydrocortisone for adults with secondary adrenal insufficiency, and no evidence was identified for prednisolone or dexamethasone, and therefore the committee made consensus recommendations based on their experience.

The committee was not able to determine the optimal dosage or timing of doses based on the evidence and agreed longer-term data would be needed to accurately

assess the cumulative benefits and any potential harms of daily treatment with hydrocortisone for adults. Glucocorticoid therapy aims to mimic the normal daily rhythm of cortisol secretion and therefore the committee recommended having 2 to 4 doses with the largest in the morning and smallest in the evening, titrating the dose to maximise wellbeing and minimise side effects. The committee noted that in people with adrenal insufficiency due to congenital adrenal hyperplasia (CAH), an increase in glucocorticoid dose may be required to reduce androgen production and specialist advice would be needed.

The evidence for dexamethasone was limited. 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 per 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 if there is poor adherence or if people have type 1 diabetes, as there can be an increased risk of hypoglycaemia especially overnight when cortisol levels are low.

The committee did not recommend the use of continuous subcutaneous hydrocortisone pumps for routine daily replacement in people with adrenal insufficiency. There was limited evidence to support their use and people would require training before being able to use the device. Also, some people have device-related adverse events such as site infections.

Prednisolone and hydrocortisone are recommended as alternative pharmacological treatments but there is no evidence comparing these preparations, or with modified-release hydrocortisone, in people with secondary or tertiary adrenal insufficiency group, therefore the committee decided to make a research recommendation.

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 fludrocortisone replacement.

Emergency management kits

Current practice on the prescription of emergency management kits is variable, so to help determine the cost effectiveness, the total cost of prescribing an initial emergency management kit was estimated. This consisted of 1 emergency dose of intramuscular hydrocortisone, the consumables to inject intramuscular hydrocortisone and the staff costs associated with training people with adrenal insufficiency (and their family and carers) on how to give emergency hydrocortisone. Fluids were not included in this cost because these are only given to people once they present in a hospital setting. Two kits are required for most people, but some may require 3, for example children with separated parents, with 1 kit being kept in each home and 1 at school. Providing emergency management kits to people with primary and secondary adrenal insufficiency, and those at high risk of adrenal crisis

with tertiary adrenal insufficiency, was found to be cost effective and would not result in significant resource impact.

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.

How the recommendations might affect practice

The recommendations on steroid replacement and hyponatraemia reflect current practice and are not expected to lead to significant changes. Current practice on prescribing emergency management kits is variable and the recommendations may lead to a change in practice by some providers.

Return to recommendations

Management during physiological stress

Pharmacological management

Recommendations 1.4.1 to 1.4.9

Why the committee made the recommendations

Because only 1 study was identified, which the committee did not think was sufficient to base recommendations on, guidelines from other organisations on the pharmacological management of physiological stress were reviewed. The quality of these guidelines was assessed using the Appraisal of Guidelines for Research and Evaluation (AGREE) II tool. Guidelines that were assessed as high quality and that included recommendations the committee wished to cross refer to were further assessed using the NICE process for assessing applicability and acceptability. Based on these assessments, the committee either made their own consensus recommendations informed by these guidelines or directly cross referred to recommendations in external guidelines.

The committee emphasised the importance of having additional supplies of glucocorticoid medication available for periods of physiological stress (covered in the

information and support section). They highlighted that some people might find it difficult to obtain additional supplies of glucocorticoids, and health professionals need to be aware of this to prevent adrenal crises.

The frequency and dose of glucocorticoids need adjusting during significant physiological stress, for example, offering an increased dose if a person has a fever or physical trauma. However, there are associated harms of increasing the dose too frequently or for prolonged periods of time because this can lead to symptoms and signs of steroid excess. The committee agreed the duration of increased dosing would vary according to the type of physiological stress and factors related to the individual. If absorption of oral glucocorticoids is difficult because of vomiting or diarrhoea, then an injection of intramuscular or intravenous hydrocortisone may be given. The committee referred to the guideline for the management of glucocorticoids during the peri-operative period by the Association of Anaesthetists, the Royal College of Physicians and the Society for Endocrinology.

The committee agreed the BSPED guideline for children was comprehensive and clearly set out. It had also achieved high scores using the AGREE tool and second stage NICE assessment. Therefore, the committee agreed not to make their own recommendations but to cross refer to the BSPED website for recommendations on sick-day dosing for babies, children and young people under 16 years of age experiencing physiological stress.

As little evidence was found the committee decided to make a research recommendation for the use of postoperative glucocorticoids for people with or at risk of adrenal insufficiency having inpatient invasive procedures.

How the recommendations might affect practice

The recommendations reflect best practice but may not be current practice for all, resulting in changes to practice for some. Although there is a cost associated with providing additional supplies of oral glucocorticoids, this cost is expected to be small relative to the cost and quality of life impact of an adrenal crisis. These recommendations are therefore not expected to have a significant resource impact.

Return to recommendations

Non-pharmacological management

Recommendations 1.4.10 to 1.4.11

Why the committee made the recommendations

No clinical evidence was identified, so the committee made recommendations to reflect best current clinical practice.

The committee confirmed that all adults with adrenal insufficiency or at risk of adrenal crisis should be provided with information on managing their condition including sick-day rules and crisis management during periods of physiological stress.

A steroid treatment card (blue card) is provided to people prescribed glucocorticoids for other medical conditions. This generally affects people with non-endocrine conditions who are on exogenous steroids where dose and duration could lead to hypothalamic-pituitary-adrenal axis suppression. The card includes guidance on minimising the risks when taking steroids 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. In best practice, people are also provided information on the use of patient-held alerts about their condition. This can include medical alert jewellery such as bracelets, and apps or mobile phone medical IDs.

How the recommendations might affect practice

The recommendations for managing periods of physiological stress largely reflect current practice and will therefore not result in a significant change.

Return to recommendations

Pregnancy care

Recommendations 1.4.12 to 1.4.20

Why the committee made the recommendations

There was limited evidence for women or people with adrenal insufficiency who are pregnant or planning pregnancy, therefore the committee made consensus

recommendations based on their experience and current practice. Continuing replacement doses of glucocorticoid and mineralocorticoid is essential in pregnancy to prevent adrenal crisis. 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 steroid doses. Clinical signs including symptoms of adrenal insufficiency, postural hypotension and hyponatraemia justify increases in replacement doses during the third trimester. 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 of the baby 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.

How the recommendations might affect practice

The recommendations for managing pregnancy largely reflect current practice and will therefore not result in a significant change. The exception to this is the management of hyperemesis gravidarum in an inpatient setting which is not happening in current practice. The committee noted that deaths have been reported following outpatient management of hyperemesis gravidarum in people with adrenal insufficiency. The committee highlighted the importance of inpatient care and noted that although this is more costly than outpatient care, the population for whom this recommendation would apply is small and therefore this should not result in a significant resource impact.

Return to recommendations

Management during psychological stress

Pharmacological management

Recommendations 1.5.1 to 1.5.3

Why the committee made the recommendations

No evidence was found, so the recommendations were made by consensus based on the experience and expert opinion of the committee.

The committee were aware that there is variation in current clinical practice on whether to adjust medication to account for 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 long-term increases were not advised. An adjustment to the dose of glucocorticoid medication has the potential to reduce the risk of harm to a person experiencing an adrenal crisis because of psychological stress. 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.

The committee agreed the BSPED guideline for children was comprehensive and clearly set out. It had also achieved high scores using the AGREE tool and second stage NICE assessment. Therefore, the committee agreed not to make their own recommendations but to cross refer to the BSPED website for recommendations on sick-day dosing for babies, children and young people under 16 years experiencing psychological stress.

How the recommendations might affect practice

There is variation in current practice, therefore for some, these recommendations could lead to a change in practice. Given the small additional cost of increasing oral steroids for 1 to 2 days during periods of acute and intense psychological or emotional stress and the potential for avoiding costly and harmful adrenal crisis, this recommendation is not expected to have a significant resource impact. The recommendation for intramuscular hydrocortisone for those experiencing a severe mental health crisis and who are unable to take oral glucocorticoids would apply to a very small proportion of people and therefore would not have a significant resource impact.

Return to recommendations

Non-pharmacological management

Recommendations 1.5.4 and 1.5.5

Why the committee made the recommendations

No evidence was identified for this review. The committee decided to make consensus recommendations to highlight the significance of psychological and emotional stress as a triggering factor for adrenal crisis, and to provide advice on accessing information and support to help reduce stress and avoid an adrenal crisis. The committee acknowledged the importance of patient support groups and organisations in providing information and support, particularly to newly diagnosed people. These groups can promote awareness about exploring adjustments that may be possible within the workplace or educational setting to help people with adrenal insufficiency to participate in everyday activities. Recommendations were made to direct people to their specialist clinical team for support and advice on self-management strategies to manage stress and anxiety, and, where needed, onward referral to NHS talking therapies or mental health services.

How the recommendations might affect practice

The recommendations reflect best practice. Where best practice is not currently implemented the recommendations cover the provision of information which will likely only involve a couple of minutes of extra staff time on top of existing patient

contact with healthcare professionals and are not expected to result in any significant change. The recommendation to consider referral or self-referral to NHS talking therapies or mental health services is in line with existing NICE guidance and is considered current practice.

Return to recommendations

When to suspect adrenal crisis

Recommendations 1.6.1 and 1.6.2

Why the committee made the recommendations

Evidence for the risk factors associated with adrenal crisis was very limited and of poor quality, so the committee used their expertise to inform the recommendations and supplement the available evidence.

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.

The committee used their clinical experience to specify the features that should raise suspicion of adrenal crisis in people who are critically unwell. They noted that hyperpigmentation was the most indicative feature and should raise clinicians' suspicions of an adrenal crisis even in the absence of any other signs or symptoms. The committee also agreed that a broader range of clinical signs and symptoms should be highlighted as indicative of adrenal crisis in people who have a known diagnosis or are at high risk of adrenal insufficiency so that treatment can be delivered as soon as possible. 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.

As no evidence was found for people taking long-term glucocorticoids, a research recommendation was made for what increases the risk of adrenal crisis and adverse hospital outcomes in this group.

How the recommendations might affect practice

The recommendations reflect current practice, so the committee agreed there would be no change in practice.

Return to recommendations

Emergency management of adrenal crisis

Recommendations 1.7.1 to 1.7.10

Why the committee made the recommendations

No research evidence was identified, so existing guidelines on emergency management of adrenal crisis were used to inform the recommendations. The quality of these guidelines was assessed using the AGREE II tool. Guidelines that were assessed as high quality and that included recommendations the committee wanted to cross refer to were further assessed using the NICE process for assessing applicability and acceptability.

The 3 essential aspects of treatment are giving hydrocortisone and fluids and ensuring that the person is rapidly transported to hospital. The former 2 were included in all of the guidelines that were reviewed on the emergency management of adrenal crises. The committee highlighted that if an adrenal crisis is suspected, treatment should be given without delay and by anyone, including the person, their families, and their carers. All adult guidelines recommended immediate intravenous administration of hydrocortisone with a further dose of hydrocortisone over the following 24 hours. The committee agreed with these recommendations but acknowledged the guidelines covered treatment in hospital so only mention the intravenous route. The committee decided to recommend either intravenous or intramuscular routes to enable anyone to administer the medication.

The committee emphasised the importance of giving parenteral fluids, noting that deaths can occur even if hydrocortisone is given but fluids are not. Guidelines suggested various protocols for sodium chloride infusion, however, they all agreed that after an initial 1 litre infusion, sodium chloride should be continued for 24 hours or until the patient is stable. The committee agreed that the main aim should be to

give the initial dose of fluids as soon as possible, ideally within 30 minutes but acknowledged that how this is delivered depends on the hospital setting.

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.

Monitoring was a key feature in all of the external guideline recommendations and most commonly included monitoring of cardiac and haemodynamic parameters. Some recommendations also included transfer to intensive care if necessary. Therefore, the committee made a recommendation to highlight the importance of caring for a person in a high-observation area with frequent monitoring. 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.

To prevent deterioration of the person's condition, aid in recovery and help to prevent further crises, a consensus recommendation was made to highlight the need for referral to a specialist endocrine team for ongoing clinical advice and support throughout admission and during the hospital stay and for identifying and treating any underlying cause of adrenal crisis.

The committee agreed the BSPED guideline for children was comprehensive and clearly set out. It had also achieved high scores using the AGREE tool and second stage NICE assessment. Therefore, the committee agreed not to make their own recommendations but to cross refer to the BSPED website recommendations for emergency management of adrenal insufficiency in babies, children and young people.

How the recommendations might affect practice

The recommendations about emergency hospital treatment for people experiencing an adrenal crisis are reflective of current practice.

Return to recommendations

Ongoing care and monitoring

Recommendations 1.8.1 to 1.8.16

Why the committee made the recommendations

No evidence was identified for ongoing care and monitoring of people with adrenal insufficiency, including those who are receiving end of life care, so the recommendations were made by expert knowledge and consensus of the committee.

The frequency of clinical reviews should vary depending on the person's needs as well as the type of adrenal insufficiency they have. People with newly diagnosed primary adrenal insufficiency may need more intensive monitoring initially until the healthcare professional is sure that a person understands the condition and how to manage it, or if the person has symptomatic adrenal insufficiency requiring more clinical management. However, adults with adrenal insufficiency who are confident with self-management and have stable clinical needs may need less frequent monitoring. The method of follow-up and monitoring would also differ according to individual needs, with face-to-face appointments more suitable for some people and telephone or video consultations for others.

It is important to monitor signs and symptoms of under- or over-replacement of glucocorticoids. Under-replacement of glucocorticoids may cause weight loss, nausea, and fatigue. It is important to investigate whether these broad, non-specific symptoms can be attributed to under-replacement of glucocorticoids or have other causes. For example, short-term fatigue may occur while a person adjusts to the treatment and would not need a change in the dosage, but sudden-onset fatigue or fatigue that significantly affects activities of daily living should not be ignored. Signs and symptoms indicating over-replacement of glucocorticoids, particularly in people on higher than standard doses, may include unexplained weight gain, new or worsening diabetes or hypertension.

An important part of reviews is to make sure that people with adrenal insufficiency understand the importance of adhering to their medication, how to avoid having an adrenal crisis and knowing what to do in emergency situations.

For children, the committee agreed that appointments with the specialist team should be at least every 6 months, but as for adults, should be adjusted according to individual needs. An annual face-to-face hospital appointment should be offered to measure the height and weight of children to ensure their condition is being well managed. The committee noted more frequent monitoring may be required during periods of rapid growth when dosages of medication may need to be changed when transitioning to adult services to facilitate a smooth handover, or if there are concerns with medicines adherence or whether the child and their family or carers are able to safely self-manage the condition.

The committee agreed that for people receiving end of life care, decisions on withdrawing active treatment should be made as part of shared decision making. This does not mean withdrawing steroids but may include changes to how medication is given, such as by injection rather than orally. The committee agreed to cross refer to the recommendations in the NICE guidelines on end of life care for adults and end of life care for infants, children, and young people with life-limiting conditions for general principles of care appropriate for people with adrenal insufficiency.

How the recommendations might affect practice

The recommendations reflect current practice and are not expected to lead to significant changes.

Return to recommendations

Managing glucocorticoid withdrawal to prevent adrenal insufficiency

Recommendations 1.9.1 to 1.9.8

Why the committee made the recommendations

The evidence available was very limited. Withdrawal interventions varied between the studies, and only 1 study covered children. Many studies looked at the withdrawal of oral prednisone, and although this is not licensed for use in the UK, the committee agreed it was relevant because withdrawal strategies for other medicines would be similar. The committee decided by consensus that outcomes specifying adrenal insufficiency as an adverse event or those which could indicate steroid withdrawal syndrome or be indicative of adrenal suppression, would aid decision making. These included: hyperkalaemia, nausea, hyponatraemia, diarrhoea, vomiting, lethargy, malaise, anorexia, and myalgia. The committee used their consensus opinion to formulate the recommendations. They discussed that in clinical practice, decisions around tapering are rarely straightforward and are decided on a case-by-case basis through assessment of individual needs. The evidence suggests that rapid tapering regimes do not lead to an increase in adverse events or incidence of adrenal insufficiency, but due to the limited evidence available, the committee were not confident in the results reported. However, they recognised the need to provide generalised guidance for non-endocrine specialist clinicians and agreed that starting with a tapering regimen that involves the following could be trialled: taking the physiological equivalent dose every other day for 2 weeks, then twice a week for 2 weeks, then stopping. The committee reasoned that this is roughly the equivalent to halving the dose for 2 weeks and then halving it again. They agreed that it is simple for people to understand and follow and has been widely used in clinical practice so there should not be any safety concerns. Glucocorticoids can also be tapered more slowly. The committee highlighted that if there are any symptoms of adrenal insufficiency or any uncertainty, glucocorticoid should be reverted to a physiological equivalent dose, and consideration given to contacting an endocrine specialist.

The committee discussed the practice of switching to different types of glucocorticoids while tapering. People should not be routinely switched from prednisone to hydrocortisone because there is no evidence to support this. The committee noted this is happening in current practice despite the lack of evidence of benefit.

The committee agreed that if people aged 16 and over are taking dexamethasone for a longer duration and have any difficulty while tapering then clinicians should consider switching to prednisolone. 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 steroid-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.

The committee noted that there is an increased chance of difficulties withdrawing glucocorticoids for people using multiple glucocorticoid preparations simultaneously, using high-dose inhaled glucocorticoids, or for those people who had intra-articular or intramuscular glucocorticoid injections in the previous 2 months, or who had treatment with strong cytochrome P450 3A4 inhibitors along with glucocorticoids.

The committee decided to make a research recommendation because very little evidence was found and there is uncertainty around how best to withdraw glucocorticoids, which can lead to overtreatment and an increased risk of adrenal insufficiency.

How the recommendations might affect practice

The recommendations on tapering regimens reflect current practice and the committee agreed there should be no significant change in practice. Because of the uncertainty in the population size and to minimise the resource impact to the NHS, the recommendations for testing in this population were restricted to those who develop signs and symptoms after trying a slow taper, as opposed to everyone withdrawing from long-term glucocorticoids and a weaker ‘consider’ recommendation was made.

Return to recommendations

Context

Adrenal insufficiency is the inadequate production of corticosteroid hormones, glucocorticoids, 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.

Adrenal insufficiency may have a considerable effect on daily living and may lead to an adrenal crisis if not identified and treated. Common causes of adrenal crisis in people with adrenal insufficiency are gastrointestinal illness (23%), other infections (25%), surgery (10%) and physiological stress (9%). An adrenal crisis is a medical emergency and can be fatal.

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

Care is variable in the UK and small numbers of people die each year from adrenal crisis. Although deaths are rare and avoidable, awareness needs to be raised about the importance of glucocorticoid replacement for people with adrenal insufficiency who are at risk of adrenal crisis. There is an adult NHS Steroid Emergency Card and paediatric BSPED Steroid Emergency Card for people at risk to carry to help ensure prompt, appropriate treatment if they have an adrenal crisis.

Better recognition of people at risk of adrenal insufficiency, and awareness of the acute- and long-term management of adrenal insufficiency, would improve patient care and quality of life, and reduce associated complications. This guideline aims to improve the management of adrenal insufficiency and the quality of life of people with adrenal insufficiency.

Finding more information and committee details

To find NICE guidance on related topics, including guidance in development, see the NICE topic page on adrenal dysfunction.

For details of the guideline committee see the committee member list.