# Adrenal Insufficiency

<table>
<thead>
<tr>
<th>Title of Guideline</th>
<th>Guideline for the Recognition and Management of children and young people with Adrenal Insufficiency/Crisis</th>
</tr>
</thead>
</table>
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Consultant in Paediatric Endocrinology & Diabetes |
| Directorate & Speciality | Directorate: Family Health – Children  
Speciality: Endocrinology |
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| Date when guideline reviewed | January 2021 |
| Guideline Number | 1929 |
| Explicit definition of patient group to which it applies (e.g. inclusion and exclusion criteria, diagnosis) | Children and Young People under age 19 years |
| Abstract | This guideline describes the risk factors, symptoms and signs and management of adrenal insufficiency |
| Key Words | Paediatrics. Children. Adrenal insufficiency, adrenal crisis, steroids. |

Statement of the evidence base of the guideline – has the guideline been peer reviewed by colleagues?

1a meta analysis of randomised controlled trials | Put a cross (X) in the highest level of evidence. |
2a at least one well-designed controlled study without randomisation |
2b at least one other type of well-designed quasi-experimental study |
3 well –designed non-experimental descriptive studies (ie comparative / correlation and case studies) | X |
4 expert committee reports or opinions and / or clinical experiences of respected authorities |
5 recommended best practise based on the clinical experience of the guideline developer |

**Consultation Process**  
Staff at Nottingham Children’s Hospital via the Guidelines E-mail process.  
**Target audience**  
Staff at the Nottingham Children’s Hospital

This guideline has been registered with the trust. However, clinical guidelines are guidelines only. The interpretation and application of clinical guidelines will remain the responsibility of the individual clinician. If in doubt contact a senior colleague or expert. Caution is advised when using guidelines after the review date.
Document Control

Document Amendment Record

<table>
<thead>
<tr>
<th>Version</th>
<th>Issue Date</th>
<th>Author</th>
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<tbody>
<tr>
<td>V1</td>
<td></td>
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<tr>
<td>V2</td>
<td>November 2014</td>
<td>Dr. Denvir</td>
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<tr>
<td>V3</td>
<td>January 2018</td>
<td>Dr. Hoong-Wei Gan</td>
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Summary of changes for new version:

Update on hypoglycaemia management in line with new sugar content of Lucozade/ Coca Cola.

Addition of standard synacthen test protocol.

Update of contact details.

Statement of Compliance with Child Health Guidelines SOP

This guideline has had only minor changes made and therefore this version has not been circulated to all for review. A previous version had been approved by circulation to senior team members.

Maria Moran
Clinical Guideline Lead
8th January 2018
Background

Adrenal insufficiency is relatively rare in children. For unknown cases the presentation can be very vague and non-specific. If unrecognised acute adrenal insufficiency precipitated by physiological stress may lead to a life-threatening crisis with acute cardiovascular collapse.

Symptoms and Signs of Adrenal Crisis

- Weakness
- Nausea, vomiting
- Abdominal pain
- Dehydration
- Hypoglycaemia
- Seizure
- Hypotension
- Shock

Clues for Diagnosis - History:

- Patient known to have adrenal insufficiency: Primary (eg. Congenital Adrenal Hyperplasia, Addison’s Disease) or Secondary (Hypothalamic/Pituitary dysfunction)

- In Infants: cortisol deficiencies will cause hypoglycaemia and jaundice, while aldosterone deficiencies will result in poor feeding, vomiting and failure to thrive.

- Patient on Exogenous Steroids: secondary adrenal insufficiency caused by abrupt discontinuation or stress while on suppressive doses. Those at risk:
  - Prednisolone > 0.3 mg/kg/day or > 10 mg / day for > 3 weeks – NB. BNF equivalent potencies relate to anti-inflammatory action not growth and adrenal suppressive action (Dexamethasone much more potent than prednisolone. Fluxotide much more potent than beclomethasone)
  - High dose inhaled steroid: > 800 micrograms/day Beclomethasone or > 400 micrograms per day Fluticasone (or equivalent)
  - Repeated courses of exogenous steroids
  - Short course of exogenous steroids within one year of cessation of long-term steroids.
    - (Morning compared to evening doses and alternate day regimes cause less adrenal suppression)

- Undiagnosed primary adrenal insufficiency may cause: chronic fatigue, anorexia, nausea, vomiting, weight loss, recurrent abdominal pain, pigmentation, behavioural changes, developmental delay or a reduction in school performance.

- Other autoimmune diseases may be a clue to the presence of Addison’s disease eg. Recurrent hypoglycaemia in a child with Type 1 diabetes mellitus.

- Undiagnosed acquired hypothalamic/pituitary disease: Craniopharyngioma or pituitary tumours, post cranial irradiation, hypothalamic or pituitary surgery. Less common causes: vascular insult, trauma and meningitis.
Clues for Diagnosis – Examination – Infants:

- Jaundice, micropenis, cranial midline defect – can be features of congenital hypopituitarism in the newborn.

- Ambiguous genitalia – virilisation, enlarged clitoris, hyperpigmented and fused labia, scrotal hyperpigmentation in congenital adrenal hyperplasia.

- Dehydration/salt wasting crisis – unrecognised congenital adrenal hyperplasia.

Clues for Diagnosis – Examination – Older Children:

- Precocious virilisation, accelerated growth and bone age – can be features of congenital adrenal hyperplasia

- Increased skin pigmentation (areolae, genitalia, scars, palmer creases, axillae, gums) – some may have loss of pubic or axillary hair.

- Orthostatic hypotension or postural tachycardia – if not frankly hypotensive.

- Signs of high dose steroid side effects (replacement steroids should not cause these side effects).

<table>
<thead>
<tr>
<th>Short Term therapy (&lt;3 weeks)</th>
<th>Long Term Therapy (&gt; 3 weeks)</th>
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<tbody>
<tr>
<td>Gastritis</td>
<td>Gastric ulcers</td>
</tr>
<tr>
<td>Growth arrest</td>
<td>Short stature</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>Weight gain</td>
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<tr>
<td>Hypercalcuiria</td>
<td>Osteoporosis</td>
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<tr>
<td>Hyperglycaemia</td>
<td>Slipped epiphyses</td>
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<tr>
<td>Immune suppression</td>
<td>Ischaemic bone necrosis</td>
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<tr>
<td>Masks inflammation</td>
<td>Raised intracranial pressure</td>
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<tr>
<td>Toxic psychosis</td>
<td>Poor wound healing</td>
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<tr>
<td>Benign intracranial pressure</td>
<td>Catabolism</td>
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<td></td>
<td>Cataracts</td>
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<td></td>
<td>Bruising</td>
</tr>
<tr>
<td>Adrenal/pituitary suppression</td>
<td>Muscle wasting</td>
</tr>
<tr>
<td></td>
<td>Toxic psychosis</td>
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</tbody>
</table>
Laboratory Findings:

- **Hypoglycaemia** – in both primary and secondary adrenal insufficiency
- **Hyponatraemia and hyperkalaemia** are features of primary adrenal insufficiency (deficiency of aldosterone secretion)
- **Hyponatraemia** may also be seen in secondary adrenal insufficiency (water retention from lack of cortisol antagonising vasopressin effect).

Investigations to Establish Diagnosis:

- **If Adrenal Crisis is suspected DO NOT wait for results before starting treatment.**
- In all patients:
  - Blood glucose bedside
  - Serum glucose and U&E
  - Blood gas
  - (A paired urine sodium may be useful, as a detectable urine sodium with a serum sodium of <125 mmol/l is diagnostic of salt-wasting)
  - In suspected new cases of adrenal insufficiency:
    - Take acute blood samples **BEFORE** administering exogenous steroid if possible. (liaise with clinical chemistry to let them know Renin, Aldosterone and ACTH are being sent and send immediately)
      - Cortisol – lithium heparin tube
      - Aldosterone – lithium heparin tube
      - Renin – EDTA tube
      - ACTH – EDTA tube
  - Also in all **infants** and in **children with precocious virilization**:
    - 17OHP (17 hydroxyprogesterone)
    - Urine for urinary steroid profile (USP)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Cortisol</th>
<th>ACTH</th>
<th>17-OH</th>
<th>Aldosterone</th>
<th>Renin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Adrenal Failure</td>
<td>↓</td>
<td>↑</td>
<td>↔</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>ACTH Deficiency (pituitary / Hypothalamus)</td>
<td>↓</td>
<td>↓</td>
<td>↔</td>
<td>↔ or ↓ (salt wasting)</td>
<td>↔ or ↑ (salt wasting)</td>
</tr>
<tr>
<td>21-Hydroxylase deficiency</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↔ or ↓ (salt wasting)</td>
<td>↔ or ↑ (salt wasting)</td>
</tr>
</tbody>
</table>

Discuss with **Endocrinology team** specific diagnostic tests in new cases.
Management of Children presenting acutely with adrenal crisis:

- **Assess A B C**
- **Obtain intravenous access** and take samples **BEFORE TREATMENT** (see above)
- **Intravenous fluid**: If signs of circulatory failure give intravenous bolus of 20 ml/kg of 0.9% saline followed by maintenance fluids (0.9% saline with 5% or 10% dextrose)
- **Intravenous hydrocortisone**: (if unable to gain intravenous access give same dose as intramuscular injection)

<table>
<thead>
<tr>
<th>Weight Range</th>
<th>Hydrocortisone Dose</th>
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<tbody>
<tr>
<td>&lt; 10Kg</td>
<td>25mg</td>
</tr>
<tr>
<td>10 – 25Kg</td>
<td>50mg</td>
</tr>
<tr>
<td>&gt;25Kg</td>
<td>100mg</td>
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</tbody>
</table>
- **Subsequent doses of hydrocortisone 6 hourly** (dose approximately 50 mg/m²/day (stress dose))
- **If hypoglycaemic (blood sugar < 2.6 mmol/L)** - investigate and treat as per hypoglycaemia guideline 9.1
- Identify and treat potential precipitating causes such as sepsis
- **Close observation** on the ward including blood pressure and Glasgow coma score
- **Strict fluid** input and output
- Regular **blood sugar** and **electrolyte** monitoring
- Fluid and electrolyte imbalance should be corrected appropriately
- Weigh child on admission and where possible compare this weight to previous recorded measures
- **In cases of combined cortisol deficiency and diabetes insipidus** close monitoring of electrolytes and fluid balance required and early discussion with paediatric endocrinology consultant on call is required.
  - **In cases of combined cortisol deficiency and hypothyroidism** (e.g. hypopituitarism) supplementation with hydrocortisone is recommended for 48 hours before starting levothyroxine as this may precipitate an adrenal crisis.

Patient should be tolerating oral fluids/medication with no diarrhoea or vomiting and have stable blood sugars and electrolytes before discharge.

*As soon as possible let the endocrine team know about all cases of suspected or known adrenal insufficiency for advice on ongoing management.*
Long-term management

Safety and Identification

All patients should wear bracelet/necklace indicating that they are at risk of adrenal insufficiency.

What to do if patient is unwell at home or presents to hospital

An individualised plan using the template – appendix 1 should be given to all patients before they leave hospital.

Monitoring of patients on replacement steroids

This will be undertaken by endocrine team. Ensure follow up in place

Monitoring of patients on long term high dose steroids

Monitor growth and blood pressure at least 3 monthly.

Educate families on symptoms and signs of hyperglycaemia and advice attendance at hospital on the same day, if these occur.

Check u+/e’s, glucose, bone profile and vitamin D status 3 monthly. Maintain corrected calcium, phosphate, magnesium in the normal range. Keep vitamin D levels > 50 nmol/L.

A regular assessment of bone mineral density is advised, only after discussion with endocrine team, and all symptoms of back pain investigated for vertebral collapse with a lateral spine xray. Bisphosphonates are the only agents of proven benefit in the management of symptomatic steroid-induced osteoporosis. Please discuss each case directly with the endocrinology team.

Withdrawal of steroids

Long-term pharmacological glucocorticoid therapy inhibits transcription of the gene(s) for glucocorticoid receptors, thus reducing the number of receptors per cell. Physiologic concentrations of glucocorticoids will elicit subphysiologic cellular responses.

Therapy for a couple of months will completely suppress the hypothalamo-pituitary-adrenal axis but will not cause adrenal atrophy. Therapy of years’ duration may result in almost total atrophy of the adrenal fasciculata/reticularis,

Never stop long-term steroids abruptly. Dose should be weaned over 3 weeks (eg by 25% weekly) if < 1 year’s treatment, more slowly over months if > 1 year’s treatment.

Remember that adrenals may remain suppressed for months to a year following withdrawal. Consider performing a standard short synacthen test (Appendix 2) pre discontinuation and then 6 months later if suboptimal. Steroid cover (hydrocortisone) may be required in the interim as replacement or for illness/surgery, depending on result. Discuss with endocrinology team pre synacthen testing and with results.

Symptoms of possible adrenal insufficiency to look for after glucocorticoid withdrawal are malaise, anorexia, headache, lethargy, nausea and fever. This symptom complex does not include salt loss, as adrenal glomerulosa function is regulated principally by the renin-angiotensin system and remains normal. However, blood pressure can fall abruptly, as glucocorticoids are required for the action of catecholamines in maintaining vascular tone.
Surgery (long term high dose and replacement steroids)

Do not omit regular glucocorticoid prior to surgery. Regular fludrocortisone is omitted until tolerating enteral intake. Inform the anaesthetist and give 2mg/kg intravenous hydrocortisone at induction. Further doses of intravenous hydrocortisone will be required 6 hourly (Stress dose equivalent to 50 mg/m²/day divided into four doses) until enteral intake tolerated. Regular oral steroid treatment should then be restarted. (Following major surgery double dose of regular replacement hydrocortisone and give four times a day for 24-48 hours). Dexamethasone may be used instead in neurosurgical patients as it has less mineralocorticoid effect (discuss with endocrinology team as doses may not need to be increased).

Management of patients with combined anterior and posterior pituitary deficiencies

In situations of cortisol insufficiency, the patient is unable to excrete a water load and where combined anterior and posterior pituitary hormone deficiencies exist and Desmopressin (DDAVP) therapy is used, there is always the danger of dilutional hyponatraemia.

In patients who are unwell and suffer with a combination of anterior and posterior pituitary defects, no further Desmopressin (DDAVP) should be given until the plasma electrolytes have been checked. Water intoxication is difficult to treat and can be dangerous. It is usually safer to under-treat the diabetes insipidus at this stage and simply replace fluid losses (see Diabetes Insipidus guideline). Strict monitoring of fluid balance and electrolytes and early discussion with the paediatric endocrinologist on call is required.

Patients with absent thirst and diabetes insipidus are amongst the highest risk group. These patients need to attend hospital, even if they are slightly ill, as their fluid balance is usually precarious.
References:

INSTRUCTIONS FOR PARENTS OF CHILDREN ON LONG TERM STEROID TREATMENT
WHAT TO DO IF YOUR CHILD IS UNWELL OR INJURED.

Patient label - stick here

Diagnosis:
Regular medication: ______________________

Effortesol ___ mg intramuscular injection for use in
illness/emergency

Date:    Age , Weight kg, Height cm, Body surface area m²

Your child is receiving steroids because of a medical condition. If your child becomes unwell, is involved in an accident, or requires surgery (either planned or as an emergency) it will be necessary for your child to increase their dose of hydrocortisone (if already on this medication) or take hydrocortisone (if not already on hydrocortisone) to be able to cope with the illness/stress adequately.

Your child should wear an identity bracelet/necklace stating that he/she is at risk of adrenal insufficiency.

1) For a minor illness with a temperature below 38 degrees celcius (such as a cough or cold): no change to above medication required.

2) For a febrile illness with a temperature more than 38 degrees celcius:

   a) Give hydrocortisone 6 hourly at a dose of ______mg per dose (= 50 mg/m²/day) until 24 hours after your child is well again.

   b) Check blood sugar frequently 2-4 hourly before sugary drinks/food and encourage frequent 1-2 hourly sugary drinks. Avoid prolonged fasting. Normal blood sugar is 3-7 mmol/L.

      ➢ If blood sugar is less than 3 mmol/L and:

         ▪ Your child is fully alert and able to swallow, give a sugary drink (= 100 - 200 ml of lucozade/coke/lemonade/fruit juice) and recheck blood sugar after 15 minutes to ensure it is increasing. If blood sugar is still less than 3 mmol/L, repeat sugary drink. If blood sugar rises above 3 mmol/L, give something more substantial to eat eg. bread, cereal and continue to monitor. If illness is not getting better within 24 hours seek same day medical review.

         ▪ Your child is drowsy/not fully alert, not able to have sugary drinks by mouth or blood sugar cannot be kept above 3 mmol/L, give intramuscular injection of hydrocortisone (Efcortesol dose ______mg) and call 999.

3) For an illness with vomiting and/or diarrhoea - medication by mouth including
hydrocortisone may not be absorbed adequately. Therefore, give intramuscular injection of hydrocortisone (Efectoresol dose ________mg) and bring to hospital for urgent review at the nearest emergency department. Check blood sugar level and if blood sugar less than 3 mmol/L follow advice in above paragraph. If not fully alert or blood sugar cannot be kept above 3 mmol/L call 999.

Advice for medical staff

Review urgently with immediate ABC observations and bedside blood sugar level. Give intramuscular hydrocortisone – dose ____mg [25mg (<10kg), 10-25kg (50mg), >25kg (100mg)] if not already given en route to hospital. Gain intravenous access and take blood for u+e’s, true blood sugar. Continue hydrocortisone at a dose of ____mg every 6 hours (= 50 mg/m²/day). Keep under observation until all observations/u+e’s/blood sugar levels are normal and stable and child is drinking normally with no ongoing diarrhoea or vomiting.

Advice is available for medical staff 24 hours a day from a paediatric endocrine consultant. Contact details below.

Contact numbers

| Dr Denvir/Randell/Sachdev’s secretary | ext 62336/62367 |
| Dr Denvir/Randell/Sachdev’s registrar | 07812269942 |
| Jo Benson/ Jacqui Alexander, Paed Endocrine Specialist Nurses | ext 65123 or bleep 7808342 |

THERE IS A PAEDIATRIC ENDOCRINE AND DIABETES CONSULTANT ON CALL FOR TELEPHONE ADVICE FOR MEDICAL STAFF 24 HOURS A DAY. CONTACT VIA QMC SWITCHBOARD – 0115 924 9924
Appendix 2

Standard Short Synacthen test

Use
To assess suspected adrenal insufficiency

Presentation
250 microgram in 1ml

Preparation
- Fasting is not required.
- All steroid therapy, other than Dexamethasone or Bethamethasone, interferes with the assay of cortisol. **Hydrocortisone therapy should have been stopped for at least 12 hours prior to the test.** Prednisone, prednisolone or other interfering therapy should have been stopped for at least 24 hours.
- If the test is being performed whilst on hydrocortisone maintenance, it is important that this is continued until a normal response is confirmed. **Don’t forget to ensure that the morning dose of hydrocortisone is given after the synacthen test** in these patients.

Dose
<table>
<thead>
<tr>
<th>Synacthen (Tetracosactrin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>&lt;6 months</td>
</tr>
<tr>
<td>6-24 months</td>
</tr>
<tr>
<td>&gt;24 months</td>
</tr>
</tbody>
</table>

Route
IM or IV (dilute in 2ml normal saline and give slowly over 2 minutes)

Procedure

<table>
<thead>
<tr>
<th>Sample</th>
<th>Cortisol (nmol/L)</th>
<th>ACTH (ng/L) (EDTA sample)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 min</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td></td>
<td><strong>Give IM or IV Synacthen</strong></td>
<td></td>
</tr>
<tr>
<td>30 min</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>60 min</td>
<td>✓</td>
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</tbody>
</table>

Precautions
Allergic reactions to synacthen have been reported, but it is extremely rare

Interpretation
1) Peak cortisol should be >420 nmol/L (NUH laboratory) or please check local lab’s reference range if test not performed at NUH and the increment should be >200nmol/L. Raised ACTH levels with impaired response suggest primary adrenal insufficiency
2) In patients who have been on long term steroid therapy, adrenal function will be suppressed, and the adrenal glands may not be stimulated during the short synacthen test, or only partially so.
3) Consider adrenal antibodies and in boys, consider very long chain fatty acid to exclude X-linked adrenoleukodystrophy (Sheffield) if primary adrenal insufficiency is suspected.