East Kent Hospitals University NHS Foundation Trust

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ADRENAL INSUFFICIENCY: GUIDELINE FOR INVESTIGATION

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Version Control Schedule

Version	Date	Author	Status	Comment
1.0	12-2013	Mrs Ruth Lapworth Dr Susan Vickery	Archived	Archived
2.0	May 2017	Mr C Rowe/Dr S Stock	Archived	Archived
3.0	Sep 2018	Mr C Rowe/Dr S Stock	Archived	Added citalopram as a drug that may interfere with the short synacthen test and HPA axis overall - reference has been added in appropriate section of document.
4.0	Nov 2022	Dr D Fan/Dr S Stock		Changed the title of the doc from 'adrenal hypofunction' to 'adrenal insufficiency' Re-structured the guideline with new background information Updated cortisol cut-offs for suggesting short synacthen test. Updated protocol for cortisol day curve and management of steroid withdrawal. Updated contraindications of using synacthen Updated interference from steroids

Consultation and Ratification Schedule

Name and Title of Individual	**Date Reviewed**
Dr C McGettigan, Consultant Endocrinologist	Oct 2022
Dr S Aftab, Consultant Endocrinologist	Sep 2022

Name of Committee	**Date Ratified**
PMGC	Nov 2022
CSS Quality and Risk Committee	Jan 2023

Contents

1. Introduction, Background and Purpose

Adrenal insufficiency is a condition in which the adrenal glands do not produce adequate amounts of steroid hormones, in particular cortisol.

In primary adrenal insufficiency (PAI; also known as Addison's disease), the destruction of adrenal cortex impairs cortisol production. The absence of cortisol leads to increased production of adrenocorticotrophic hormone (ACTH) because negative feedback to the pituitary gland is reduced. The most common cause of PAI is autoimmunity (up to 90% in western countries) in adults, followed by infectious diseases such as tuberculosis, adrenalectomy, neoplasia, genetic causes and iatrogenic factors. Congenital adrenal hyperplasia (CAH) is the commonest cause in children.

Secondary adrenal insufficiency occurs when pituitary ACTH production is insufficient; this leads to adrenal atrophy. Causes include intracranial disorders, such as pituitary tumour, subarachnoid haemorrhage, and traumatic brain injury, or treatment for pituitary diseases. In long-standing secondary failure the adrenals may also demonstrate an impaired response to stimulation. There is evidence that use of acute and chronic opioid therapy can cause significant secondary adrenal insufficiency. The insufficiency is usually reversible after discontinuation of opioid therapy. These patients may demonstrate a suppressed basal cortisol and ACTH and a blunted cortisol response to synacthen.

Tertiary adrenal insufficiency results from disruption to the production of corticotropin-releasing hormone (CRH) from the hypothalamus, which affects ACTH production from the anterior pituitary. Causes include treatment for tumours in the hypothalamus or adjoining structures, or more commonly administration of glucocorticoids for more than 4 weeks causing hypothalamic-pituitary-adrenal axis [HPA-axis] suppression.

Typical symptoms and signs of adrenal insufficiency including hyponatraemia, hypotension and hypoglycaemia result from the deficiency of cortisol and in some cases mineralocorticoids. Adrenal insufficiency can present as a chronic condition or acutely (Addisonian crisis) and responds to steroid replacement therapy. If left untreated, adrenal crisis can be fatal due to the central role of these hormones in energy, salt, and fluid homeostasis.

2. Definitions

ACTH	adrenocorticotrophic hormone
HPA axis	hypothalamic-pituitary-adrenal axis
PAI	primary adrenal insufficiency
Synacthen	synthetic ACTH (Tetracosactide)
CAH	Congenital adrenal hyperplasia
CRH	Corticotrophin releasing hormone

3. Scope

This guideline outlines the clinical investigation required to confirm or exclude a diagnosis of adrenal insufficiency. It may be used for patients both within the Trust and in primary care and the community.

4. Guidance

All staff involved in the investigation of adrenal insufficiency, whether clinical or laboratory, must adhere to this guideline. As with any other laboratory investigations, full and explicit clinical details must be included with all requests, which enable interpretation and maximise potential benefit to the patient. All requests are subject to review within the laboratory and inappropriate requests, or those lacking clinical information, may not be processed.

4.1 Adrenal insufficiency: guidelines for investigation

A. Suspecting adrenal insufficiency

Many of the symptoms and signs of primary and secondary adrenal insufficiency are similar (Table 2), but there are some characteristic symptoms and signs of one or the other that should focus suspicion on either the adrenal cortex or the pituitary and hypothalamus.

Primary and secondary adrenal insufficiency
• Tiredness, weakness, mental depression • Anorexia, weight loss • Dizziness, orthostatic hypotension • Nausea, vomiting, diarrhoea • Hyponatremia, hypoglycaemia, mild normocytic anaemia, lymphocytosis, eosinophilia
Primary adrenal insufficiency and associated disorders
• Hyperpigmentation • Hyperkalaemia • Vitiligo • Autoimmune thyroid disease • Central nervous system symptoms in adrenomyeloneuropathy
Secondary adrenal insufficiency and associated disorders
• Pale skin without marked anaemia • Amenorrhea, decreased libido and potency • Scanty axillary and pubic hair • Small testicles • Secondary hypothyroidism • Prepubertal growth deficit, delayed puberty • Headache, visual symptoms • Diabetes insipidus

Table 1. Clinical manifestations of adrenal insufficiency (13)

(i) In acute setting

Primary adrenal insufficiency (PAI) should be excluded in acutely ill patients with otherwise unexplained symptoms or signs suggestive of PAI (12). Common causes of adrenal crisis include gastrointestinal illness, other infections, surgery and physiological stress.

Adrenal crisis is a medical emergency and can be fatal, so patients would require immediate therapy with iv hydrocortisone at an appropriate stress dose prior to the availability of any

test results. Diagnostic samples should be collected before the immediate therapy with iv hydrocortisone (12).

(ii) In routine (non-emergency) setting

Seek specialist advice from an endocrinologist before obtaining blood for cortisol measurement in:

- People who work night shifts with disturbed sleeping patterns

It is uncertain when the best time to obtain a serum cortisol concentration is, and interpretation of the results can be difficult.

- People receiving long-term corticosteroid treatment

Interpretation of results can be difficult, since all steroids interfere with test, either through interfering analytically with the cortisol assay (such as hydrocortisone) or through physiological response to steroids (such as dexamethasone).

- People receiving oestrogen treatment

Results may be difficult to interpret because oestrogens increase hepatic production of cortisol-binding globulin (CBG), and therefore increase cortisol concentrations.

- People with cirrhosis, nephrotic syndrome, those who are in the immediate postoperative period or who require intensive care,

Results may be difficult to interpret due to low circulating CBG or albumin, and hence, lower cortisol concentrations.

B. To establish the diagnosis

(i) Measurement of serum cortisol

In adults, if adrenal insufficiency is suspected on the basis of clinical features, request a serum cortisol and ECR profile (i.e. creatinine and electrolytes)

State on the request all relevant clinical details and that adrenal insufficiency is suspected. In patients with severe adrenal insufficiency symptoms or adrenal crisis, if clinical condition allows, hydrocortisone should ideally be started after collecting an urgent next day morning (ideally 09:00) paired cortisol and ACTH (protocol for ACTH collection is described in section 4.3).

Measurement of random serum cortisol concentrations (i.e. outside 08:00 – 10:00) are of limited value for assessment of the HPA axis unless an Addisonian crisis is suspected.

Patient preparation and consideration:

Analytically, hydrocortisone, fludrocortisone and prednisolone interfere with the cortisol assay used in EKHUFT, with cross reactivity of 100%, 36.6% and 12.3% respectively. Steroids can also interfere with the cortisol test through the physiological response to steroids (e.g. dexamethasone and prednisolone). Ensure the patient is not receiving any interfering steroids unless in an emergency diagnostic situations.

Oral oestrogen therapy should be stopped 6 weeks prior to test.
Avoid stress.

Procedure

- Collect a morning (ideally 09:00) 4 mL blood sample (gold tube) for serum cortisol.
- Clearly state on the sample tubes the actual time the blood was collected.

Interpretation:

A serum cortisol concentration >480 nmol/L excludes adrenal insufficiency assuming the patient is not receiving steroids (including HRT and hormonal contraceptives containing oestrogen). A cortisol concentration of <480 nmol/L does not exclude adrenal insufficiency, however, the diagnosis is unlikely in a patient with a cortisol of >340 nmol/L.

A morning (08:00-10:00) cortisol below 100 nmol/L in a patient that has not been on steroid treatment (oral/IM/IV) would indicate adrenal insufficiency. Seek urgent advice from an endocrinologist.

A very low (random i.e. outside 08:00-10:00) cortisol concentration (i.e. <50 nmol/L) may indicate adrenal insufficiency. Seek urgent advice from an endocrinologist, if there is high suspicion of adrenal insufficiency, including postural hypotension and/or electrolyte disturbance (i.e. low Na <125 mmol/L),

(ii) Short synacthen test (ACTH stimulation test)

A short synacthen test is indicated if there is strong clinical suspicion of adrenal insufficiency. This test is carried out as described in section 4.2.

If short synacthen is normal, but the patient presents with symptoms and signs of adrenal insufficiency, determination of renin and aldosterone can be of diagnostic value. An elevated plasma renin activity or concentration in combination with an inappropriately normal or low aldosterone concentration is suggestive of PAI (12).

C. Differential diagnosis of adrenal insufficiency

ACTH can help differentiate primary from secondary adrenal insufficiency. This test is carried out as described in section 4.3.

For secondary adrenal insufficiency, measurement of pituitary hormones including prolactin, thyroid function tests, FSH, LH and IGF-1 are also indicated.

D. Patients receiving steroid replacement therapy

Measuring cortisol concentration in patients receiving hydrocortisone steroid replacement therapy may be of value to ensure optimal replacement and the procedures in section 4.4 should be followed.

For patients who are being considered for steroid withdrawal, careful assessment of adrenal reserve is required and the procedures in section 4.5 should be followed.

E. Determination of the cause of adrenal insufficiency in secondary care

Additional investigations to determine the cause of adrenal insufficiency may include:

- Adrenal autoantibody— Autoantibodies to steroid 21-hydroxylase (21-OH) are a major component of adrenal cortex antibodies and are characteristic of autoimmune PAI. If the 21-OH antibodies are negative, males with adrenal insufficiency should be tested for adrenoleukodystrophy with plasma very long chain fatty acid (VLCFAs) (12).

- Imaging — computed tomography (CT) or magnetic resonance imaging (MRI) is not usually required if autoimmune adrenalitis is likely, but it may be requested if tuberculosis or other infection, haemorrhage, infiltration, or neoplastic disease is suspected.

- Genetic diseases in which ACTH is chronically elevated result in bilateral adrenal enlargement and should be considered in select cases (12)

4.2 Short synacthen test

Indications for test

A short synacthen test is performed for the diagnosis/exclusion of adrenal insufficiency (including Addisonian crisis). A short synacthen test is indicated if morning (08:00 -10:00) cortisol is < 340 nmol/L and there is high clinical suspicion of adrenal insufficiency e.g. due to hyponatraemia, postural hypotension, pigmentation, known primary autoimmune disease or pituitary disease.

Where there is a high clinical suspicion of adrenal insufficiency as stated above in a patient with a morning (08:00-10:00) cortisol of 340 nmol/L – 480 nmol/L, contact Duty Biochemist on 01233 616060 (x723 6060/6287) to discuss prior to performing a short synacthen test. A short synacthen test is indicated in particular for those patients who are due to start thyroxine for hypothyroidism or who are likely to have autoimmune adrenal insufficiency.

Contraindications

The short synacthen test is contraindicated in patients with known hypersensitivity to synacthen (Tetracosactide) and/or ACTH.

Patient preparation and consideration:

[as described in section 4.1 B (i)]. In addition, the short synacthen test should not be performed within the two weeks following pituitary surgery due to unreliable results.

Procedure

- For adults obtain 250 µg/mL synacthen (Tetracosactide) from pharmacy.
- For children see Specialist Paediatric Biochemical Investigations protocol (BIO NO 399). This is available on Q Pulse and within the healthcare professionals zone of Trustnet.
- This test can be performed at any time of day, as the post-stimulation value is used for diagnostic purposes.
- Firstly, order the synacthen test on Sunrise and print off the request form.
- Take blood sample (gold tube) for serum cortisol prior to synacthen injection (time 0). Write actual time on both the sample and the form.
- Inject 250 microgram synacthen i.m. or i.v. as a single dose.

- Take second blood sample (gold tube) for serum cortisol exactly 30 minutes post synacthen injection. Write actual time on both the sample and the form.
- Send both blood samples together to the laboratory with the request form for a short synacthen test.
- It is not necessary to collect a sample at 60 minutes post synacthen administration. Samples collected at this time point have no diagnostic value.

Interpretation

The interpretation of the synacthen test is based on the sample 30 minutes post-synacthen administration (table below) and assumes the patient is not on interfering drugs such as steroids (including HRT and oral contraceptives), some antidepressants and opioids.

Serum cortisol concentration (t = 30 minutes)	
> 480 nmol/L	An adequate response and excludes primary adrenal insufficiency. Note: A normal response does not exclude secondary (pituitary) adrenal insufficiency. If secondary adrenal insufficiency is suspected refer to a consultant endocrinologist
between 430 and 480 nmol/L	An equivocal response and may require further assessment of adrenal reserve after discussion with a consultant endocrinologist
<430 nmol/L	An inadequate response that suggests adrenal insufficiency. Check samples were taken after synacthen administration. If indicated, further investigation may include measurement of ACTH and cortisol in paired samples taken at 09:00.

Patients who have been receiving long-term steroid replacement may also demonstrate an inadequate response to synacthen.

Patients on opioid therapy or citalopram may demonstrate an inadequate response to synacthen due to the effect of the drugs on the HPA axis.

Altered cortisol binding in some clinical situations including patients on oral contraceptives, post-operative patients, critical illness, severe liver disease and nephrotic syndrome may make synacthen tests difficult to interpret.

4.3 ACTH: guidelines for requesting in suspected adrenal insufficiency

Indications for test

Adrenocorticotrophic hormone (ACTH) measurement is indicated for the differential diagnosis of adrenal insufficiency in patients who have demonstrated an inadequate/equivocal response to synacthen. In patient who has demonstrated an adequate response to synacthen, ACTH is indicated if patients present with high suspicion of adrenal insufficiency and pituitary/hypothalamus disease is suspected.

ACTH should not be used as a screening test. An exception is in patients with high suspicion of adrenal insufficiency, prior to the administration of steroids or prior to a synacthen test, an EDTA sample could be collected for ACTH. This ACTH sample will be saved by the laboratory and only processed in case of a failed synacthen test.

Patient preparation and consideration:

[As described in section 4.1 B (i)]. Avoid stress.

Procedure:

- Blood samples for ACTH cannot be collected in primary care, as the sample must arrive in the laboratory immediately after collection.
- Collect a morning blood sample, ideally at 09:00.
- Take a 4 mL blood sample into an EDTA tube (purple tube) for measurement of ACTH and a paired 4 mL blood sample (gold tube) for serum cortisol.
- Clearly state on the sample tubes (and the request form if available) the actual time the blood was collected.
- Send both blood samples with a request form for ACTH and cortisol to the laboratory immediately. Samples for ACTH must reach the laboratory within 10 minutes of collection. Samples that are haemolysed or not separated in time are unsuitable for analysis.
- Measurement of ACTH is undertaken at a referral laboratory.
- Requests will be vetted by the Duty Biochemist, taking into account the concurrent cortisol concentration and the response to synacthen, where known. Ensure all relevant clinical details are provided.
- The turnaround time for ACTH results is 2-3 weeks.

Interpretation:

In patients with confirmed cortisol deficiency, a plasma ACTH >2-fold the upper limit of the reference range is consistent with PAI (12).

ACTH concentration will be inappropriately low relative to the serum cortisol concentration in secondary (pituitary) or tertiary (hypothalamic) adrenal insufficiency.

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4.4 Monitoring patients on replacement steroid therapy

Indications

Measurement of serum cortisol concentration may be useful in patients receiving hydrocortisone steroid therapy. This is only indicated in patients where the replacement steroid is hydrocortisone. Day curves to assess adequacy of glucocorticoid replacement are not generally indicated and should only be undertaken in patients under the care of an endocrinologist.

Patient Preparation

Stop all oestrogen therapy 6 weeks prior to test. No fasting requirements. Patients should continue to take hydrocortisone as usual throughout the test, noting down the exact time when taking the dose.

Procedure

The following procedure is recommended unless otherwise agreed with consultant endocrinologist

Minutes	Time scale in the day curve	Test (sample type)
0	• Baseline (09:00)	Cortisol (1 X yellow top)
Patient should take AM dose of hydrocortisone as normal		
60	• Post-AM dose	Cortisol (1 X yellow top)
180	• Pre-lunchtime	Cortisol (1 X yellow top)
Patient should take Lunchtime dose of hydrocortisone as normal		
240	• Post lunchtime dose	Cortisol (1 X yellow top)
420	• Pre-PM dose (16:00)	Cortisol (1 X yellow top)
Patient should take PM dose of hydrocortisone as normal		
480	• Post-PM dose	Cortisol (1 X yellow top)

- Remember to label all blood samples and request forms with date and correct time of sample collection.
- Send each blood sample to the laboratory within 4 hours of venepuncture along with the associated request form.

Interpretation

Assessment of adequacy of hydrocortisone replacement, based on the above serum cortisol measurements, is made by a consultant endocrinologist.

4.5 Assessment of adrenal reserve: management of steroid withdrawal

Indications

Patients who are receiving a prednisolone dose <5 mg per day and are being considered for withdrawal may require assessment of adrenal reserve. Adrenal insufficiency is common in patients who are having long-term steroids slowly withdrawn

Patient preparation and consideration:

[As described in section 4.1 B (i)].

Ideally, patients should be switched to hydrocortisone first due to its short half-life before the assessment. Steroid therapy can be recommenced immediately after blood sample taken for cortisol.

Procedure

- Omit the morning dose of corticosteroid.
- Take a morning blood sample (gold tube), ideally at 09:00, for serum cortisol.

Interpretation

See section 4.1 B (i) for the interpretation of serum cortisol concentration.

If an equivocal serum cortisol concentration is obtained, a short synacthen test (see section 4.2) may be performed (NB again omitting morning dose of hydrocortisone on day of short synacthen test). If a patient is on long-term steroid therapy consider a depot (1 mg) synacthen test) (details see section 4.6).

NB If cortisol is measured in patients who have taken hydrocortisone, fludrocortisone or prednisolone at the time of testing, falsely high cortisol concentrations will be obtained due to cross-reactivity in the assay.

4.6 Depot (1 mg) synacthen test

Indications for test

Depot (1 mg) synacthen tests are generally not recommended but may be undertaken in a small number of patients if specifically requested by a consultant endocrinologist.

5 Consultation and Approval

East Kent Hospitals University NHS Foundation Trust is the key stakeholder for this guideline.

Consultation has been through e-mail communication between clinical biochemistry staff and Diabetes & Endocrinology Consultants (including Dr C McGettigan, Dr E Grigoras and Dr L Faghahati, Dr S Joseph and Dr S Aftab). Email correspondence is stored on Q-pulse

6 Review and Revision Arrangements

Two years from implementation date, by author.

7 Training

TrustNet, by proactive implementation through the Care Groups by appropriate clinical leads and by proactive dissemination to primary care partners

8 Document Control including Archiving Arrangements

Archive of this document will be through QPulse.

9 Monitoring

Within the Trust, compliance with this guideline must rest with the requesting Care Groups with vetting of requests in Clinical Biochemistry. Compliance will also be subject to occasional audit within Clinical Biochemistry.

10 References and Associated Documents

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