

Protocol for Hypoadrenalism / Addison's Disease



Relevance

This protocol is relevant to all diagnosing clinicians, ie GPs and Nurses. HCAs and other staff should be aware of the possible 'presenting symptoms' and suggest that patients see a diagnosing clinician for further investigation.

Presenting Symptoms

Adrenal insufficiency is caused by either primary adrenal failure (mostly due to autoimmune adrenalitis) or by hypothalamic-pituitary impairment of the corticotrophic axis (predominantly due to pituitary disease). It is a rare disease, but is life threatening when overlooked.

Beginning a Diagnosis

Main presenting symptoms such as fatigue, anorexia, and weight loss are nonspecific, thus diagnosis is often delayed. The diagnostic workup is well established but some pitfalls remain, particularly in the identification of secondary and tertiary adrenal insufficiency.

Patients may also present with critical or emergency symptoms of hypoadrenalism. The Physician should immediately arrange emergency admission to hospital.

When patients present with mild to moderate symptoms of possible hypoadrenalism, the GP should order early morning cortisol levels (8am – 9am fasting cortisol) along with FBC, B12, Folic Acid, Ferritin, TSH, T3, T4, Parathyroid hormone, Vitamin D, U&Es, Liver Function, blood glucose etc; in order to differentially or concurrently diagnose ME, CFS, fibromyalgia, MS-like presentation, depression, psychosis, B12 deficiency, myxedema etc.

Symptoms to consider when making a diagnosis are listed in Appendix A. The table from Appendix A can be used to complete a work-up of symptoms, which with the cortisol level estimation, allows the clinician to make a provisional diagnosis. More detail for each stage is given in this protocol to assist diagnosis and treatment. A 'consent to treatment' form is included on the back of Appendix A.

The most important/ frequent symptoms are:

- Feels faint, dizzy, headache
- Weakness, fatigue
- Anorexia, weight loss
- Abdominal pain, salt craving
- Loss of muscle mass
- Breathlessness

Diagnosis table from Appendix A – please circle condition and cortisol level to diagnose stage

	Stage 1 Preclinical	Stage 2 Preclinical	Stage 3 Subtle/ subclinical	Stage 4 Clinically significant	Stage 5 Clinically Critical	Stage 6 Clinical Emergency
Signs and Symptoms	Mild	Mild to Moderate	Moderate	Significant	Critical	Emergency (adrenal crisis)
Cortisol (blood level)	400-500 nmol/L	300-400 nmol/L	150-300 nmol/L	50-150 nmol/L	25-50 nmol/L	0-25 nmol/L

Stage 1 hypoadrenalism: Pre clinical

8-9 AM cortisol 400-500nmols/L ≈20% adrenal cortical damage ¹	<ul style="list-style-type: none"> a) Signs and Symptoms mild. b) Patient has a history of B12 Deficiency and/or presence of other Auto-immune poly-endocrine conditions (APS). c) Family history of B12 Deficiency and presence of other Auto Immune conditions.
Clinically review with 8-9 AM serum cortisol 6 monthly	

Treatment

No replacement treatment offered.

Clinically review with 8-9am cortisol level 6 to 12 monthly.

Continue to treat appropriately and adequately other co-existing autoimmune conditions (Myxedema, B12 deficiency, diabetes etc).

If Vitamin D deficient, provide appropriate vitamin D replacement therapy.

Stage 2 Pre-clinical and Primary Prevention

8-9 AM cortisol 300-400nmols/L ≈20-40% adrenal cortical damage	<ul style="list-style-type: none"> a) Signs and Symptoms mild to moderate b) Patient has a history of B12 Deficiency and/or presence of other Auto-immune poly-endocrine conditions (APS). c) Family history of B12 Deficiency and presence of other Auto Immune conditions. d) Cortisol level dropping, signs and symptoms worsening
Clinically review with 8-9 AM serum cortisol 2 monthly	

Treatment

3 months Therapeutic trial of physiological doses of:-

Hydrocortisone - 10mg 7am, 5mg 12 noon, 2.5mg 5pm (17.5mg per day) OR

Prednisolone - 2mg 7am, 1mg 12 noon, 1mg 5pm (4mg per day) Equivalent to 16mg of Hydrocortisone per day.

After the therapeutic trial, adjust the daily dose between 15-25mg as per clinical requirement:-

- Check the early morning Cortisol level prior to the 7am oral Hydrocortisone or Prednisolone dose. On the day of early morning cortisol blood testing, the first treatment dose has to be delayed according to the timing of the appointment
 - Check cortisol level the same day, 3 hours after taking the first dose of Hydrocortisone/ Prednisolone.
 - Half life of Hydrocortisone 3 hours.
 - Half life of Prednisolone up to 6 hours.
- If the level has risen well above 400-500nmols/L AND if signs and symptoms improve:-
Reduce the doses to half in 3 months then to nil by 6 months.
Clinically follow up with 8-9AM cortisol level 6 monthly or yearly, all in consultation with the patient.
If the normal circadian levels (hydrocortisone day curve) are maintained no further replacement will be required.

¹ The level of adrenal cortical damage is an estimate based on symptoms. Actual damage is not easy to measure

- Continue to treat appropriately or adequately other co-existing auto immune conditions (hypo/hyper Thyroidism, B12 deficiency, Diabetes, Hypo/hyper-parathyroidism, polycystic ovarian disease etc. Replace vitamin D if vitamin D deficient.



Stage 3: Subtle / subclinical manifestation of hypoadrenalism

8-9 AM cortisol 150-300nmols/L ≈40-60% adrenal cortical damage	<ul style="list-style-type: none"> a) Signs and Symptoms moderate. b) Patient has a history of B12 Deficiency and/or presence of other Auto Immune Poly-endocrine disorders (APS). c) Strong family history of B12 Deficiency and presence of other Auto Immune conditions.
ACTH - low/normal/high	
Aldosterone – normal/low DHEA – low/normal	

Treatment

Appropriate replacement treatment prescribed. Repeat bloods and 8-9am cortisol each month and clinically review.

If the cortisol level is steadily declining and sign and symptoms worsening -

Option 1) Refer to Endocrinologist.

Option 2) If the patient declines specialist referral and request primary care intervention: commence **physiological** doses of Hydrocortisone or Prednisolone.

Option 3) Shared care – refer to Endocrinologist and commence physiological doses of steroids and closely monitor the response by carrying out HCDC.

	7 am	12 noon	5 pm
Hydrocortisone	10mg	10mg	5mg
OR Prednisolone	2mg/3mg	2mg/3mg	1mg
<p><i>Hydrocortisone is the generally preferred replacement treatment. 1mg of Prednisolone is equivalent to 4mg of Hydrocortisone.</i></p> <p>Hydrocortisone - Peak blood level in 3 hours. Prednisolone has a longer half-life.</p>			

Hydrocortisone day curve (HCDC) in primary care setting

HCDC can be useful to assess the level of serum cortisol during the day (wakeful hours)

Within 30 minutes of waking, cortisol level should be at its highest (500-700 nmols/L)

- Initially measure cortisol level before the first daily dose (usually 7am) (no steroids taken since 5pm the previous day)
- Second sample is taken 3 hours after the 1st dose (10am)
- The third sample can be taken at 3pm (3 hours following the midday dose).
- A fourth sample can be taken at 8pm if desired.

If all the four levels are close to or just below the Circadian Rhythm Values, the patient's cortisol replacement dosing will be the optimum physiological dosing. Being physiological dosing any possibility of adrenal suppression is reassuringly prevented from ever taking place. Other adverse side effects for e.g. Gastric Ulcer, Osteoporosis, iatrogenic cushionoid syndrome, etc are also avoided.

Review and repeat the above, 3 monthly.

If the levels are beginning to rise above the Circadian Curve reduce the doses accordingly. There are occasions when cortical cells can regenerate and return to normal function. If this happens gradually reduce and eventually stop the steroid replacement therapy.

Clinically follow up these patients biannually or annually by recording absence or re-emergence of signs and symptoms and normal or diminishing cortisol levels, in close relation to the state of functioning of their adrenal glands.



Please note –

The very first day the patient presents to a clinician is most critical; because that day is the “Window of opportunity” to diagnose, treat and prevent impending irreversible damage.

Stage 4 - Clinically significant hypoadrenalism

8-9 AM cortisol 50-150nmols/L ≈60-80% adrenal cortical damage ACTH - normal/low/high Aldosterone - normal/low DHEA – normal/low	a) Signs and Symptoms severe b) Patient has a history of B12 Deficiency and/or presence of other Auto Immune Poly-endocrine disorders (APS). c) Strong family history of B12 Deficiency and presence of other Auto Immune conditions.
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Treatment

Correct Aldosterone and DHEA deficiency appropriately

Clinically review 1 weekly – if early morning cortisol level is low (50-150nmol/L) even though signs and symptoms are only moderate repeat early morning serum cortisol weekly.

IF cortisol level continues to be low:

Either choose **Option 1** – refer to Endocrinologist. **OR**

Option 2 – Commence oral physiological doses of Hydrocortisone or Prednisolone. Also provide parenteral Hydrocortisone 100mg for self-administration in an emergency. Steroid card and information leaflet etc. are provided.

Prior to hospital investigations patient will be advised to stay off oral steroids for 24, 48, or 72 hours. Please note Insulin tolerance test is not recommended for a strongly suspected Hypoadrenal patient.

Option 3 - If the patient prefers primary/secondary care (shared care) management, follow Option 3 in Stage 3 of this condition

- a) Commence physiological dose of hydrocortisone OR prednisolone. Also carryout HCDC assessment in the Primary Care setting in order to achieve optimum replacement levels.
- b) Refer to Endocrinologist the same time

Stage 5 Clinically critical hypoadrenalism

8-9 AM cortisol 25-50nmol/L ≈80-95% cortical damage	Signs and symptoms severe. Patient not critically ill however requires immediate intervention by the GP.
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Treatment

Refer to Endocrinologist under 2 week rule.

Administer 100mg hydrocortisone IV. Commence physiological doses of oral hydrocortisone/Prednisolone

	7 am	12 noon	5 pm
Hydrocortisone	20mg	20mg	5-10mg *
OR Prednisolone	5mg	5mg	2.5mg *

* Adjusting up or down according to response

Stage 6: Clinical emergency (adrenal crisis)

<p>8-9 AM cortisol 0-25nmols/L ≈80-95% cortical damage</p>	<p>Signs and symptoms:</p> <ul style="list-style-type: none"> • patient collapse, semiconscious/ unconscious, • unable to self-inject emergency hydrocortisone. • Patient critically ill.
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Treatment

Administer 100mg of Hydrocortisone IV or 100mg Efcortisol IV.

999 ambulance admission blue light.

Alert the crew/hospital. Provide ambulance crew with emergency guidelines re: adrenal crisis management, IV fluids (saline) and IV Hydrocortisone administration etc.

On hospital discharge continue therapeutic/ physiological doses of hydrocortisone as recommended by the endocrinologist.

	7 am	12 noon	5 pm
Hydrocortisone	10mg - 20mg	10mg - 20mg	2.5 - 10mg
Prednisolone	3mg - 5mg	3mg - 5mg	1 - 2.5mg

- 1) Prescribe IM/IV Hydrocortisone 100mg (5 amples) for self-administration or by a relative or friend. Syringes and needles provided.
- 2) Steroid card completed and given to patient.
- 3) Medic alert Hypoadrenalism/Addison's bracelet (patient to obtain (www.medicalert.org.uk or www.addisons.org.uk).
- 4) Patient information leaflet.
- 5) Patient, partner, friend shown how to administer the injection.

Review

- Clinically review – 1 to 3 monthly with AM cortisol level and HCDC values.
- Continue to treat appropriately and adequately other co-existing Auto-Immune conditions (Hypo / Hyper Thyroidism, B12 Deficiency, Diabetes, Hypo-Hyper Parathyroidism etc.
- If vitamin D deficient, provide appropriate vitamin D therapy.

Appendix A – Hypoadrenalism (Addison’s Disease) signs and symptoms

A quick score will reveal if hypoadrenalism is a possible diagnoses, and if the physician should order further tests.

This should be completed by the patient – it is sometimes helpful to circle the actual symptom experienced.

Name _____ DOB _____ Date _____

Where will you grade these symptoms 1-10 and circle most relevant symptoms? 1 indicates that this symptom is mild and infrequent. 10 indicates the patient has it all the time and it is severe and debilitating. A score of 5 indicates that the patient has the symptom and it affects their daily life to a moderate extent.

Joint & muscle pain/weakness	
Increased pigmentation of the skin – due to raised ACTH level (not in all cases) pigmentation may be accompanied by vitiligo	
Intermittent abdominal pain and salt craving	
Vague stomach ache or other gut symptoms, diarrhoea & nausea	
Experiences weakness, fatigue, anorexia and weight loss	
Feels faint, dizzy & headache	
Signs & Symptoms Usually subtle	
Depression/Anger/Difficulty concentrating	
Decrease in axillary and pubic hair – common in women – Alopecia	
Loss of muscle mass	
Neuropathy, Myopathy	
Dizziness, Unsteadiness, Falls, Syncope	
Breathlessness, Difficulty with speech, Chest pain	
Postural hypotension, Hyponatremia (low sodium)	
Impotence & Amenorrhoea	
Hypoglycaemia	

Diagnosis.

- Before making a provisional diagnosis of Hypoadrenalism, excluding all other possible diagnosis with appropriate blood test and investigations as clinically indicated.
- Physician should also order blood tests including FBC, B12, Folic Acid, Ferritin, TSH, T3, T4, Vit D in the following cases (ME, CFS, fibromyalgia, MS like presentation, depression, psychosis, B12 Deficiency & Myxoedema Etc).

Diagnosis (circle)

	Stage 1 Preclinical	Stage 2 Preclinical	Stage 3 Subtle	Stage 4 Clinically significant	Stage 5 Clinically Critical	Stage 6 Clinical Emergency
Signs and Symptoms	Mild	Mild to Moderate	Moderate	Significant	Critical	Emergency (adrenal crisis)
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Hypoadrenalism (Addison's Disease) Consent Form



Dear Patient

Your blood test shows that you have low levels of Cortisol in your body. Cortisol is most essential for life. Cortisol is produced by the adrenal glands. Under activity of the adrenal gland is called HYPOADRENALISM. Many of the symptoms of hypoadrenalism are due to a deficiency of the steroid hormone cortisol.

The deficiency can be corrected effectively in all stages of its presentation.

Treatment

Usually the treatment will be oral steroid tablets for some patients, we may offer an Emergency Pack including an injection for use by family member or friends. In this case training will be given.

It is most beneficial and safe for the patient, if the deficiency is corrected promptly in the very early stages of its presentations.

Treatment:

Oral steroid tablets are taken by mouth. In emergencies; injection form has to be used by self or by a family member or a friend.

Side effects:

You are given safe physiological doses of cortisol just to correct the deficiency. The dose will be adjusted following periodic blood tests so that the level of cortisol is kept just below the normal cortisol day curve level. Therefore you will not experience any side effects from the replacement therapy.

The Practice has explained

About the condition

Treatment required and ongoing monitoring

I fully understand and I accept the above:

Signature:

Date:

For Surgery Information:

Additional Requirements

- Signs & Symptoms sheet completed..... []
- Consent form signed..... []
- Steroid card given..... []
- Patient Information Leaflets given..... []
- IM/IV hydrocortisone 100ng or efcortisol prescribed..... []
- Syringes/needles etc provided..... []
- Self injecting training given..... []

e-mail info@addisons.org.uk Website www.addisons.org.uk
www.medicalert.org.uk – to obtain Addison's/hypoadrenalism bracelet