Appendix 1: Protocol for excluding B12 deficiency (Megaloblastic anaemia/Pernicious anaemia) from adult and child patient presentation

Relevance

This protocol is relevant to all diagnosing clinicians, i.e. 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

If a patient presents with **Tiredness, depression, hair loss, pins and needles, numbness in hands or feet, tremors and palsies, palpitations, recurrent headache or dizziness**, B12 deficiency should be considered.

Beginning a diagnosis – presenting to GP/ Nurse

Using the **One Minute Health Check on page 271**

If B12 deficiency is suspected order a blood test for FBC, Serum vitamin B12, Folic Acid, TSH, U+Es, LFT, Serum ferritin, Glucose, 8-9am cortisol, Vitamin D to confirm/ exclude the most common conditions found alongside Vitamin B12 deficiency. Other appropriate diagnostic tests at this point include parathyroid, adrenal and ovarian hormone tests.

Refer to Appendix B for diagnosis and treatment and await blood results if appropriate. Note that for patients with severe Signs and Symptoms, treatment may need to be initiated without waiting for the results of blood tests.

Once blood results are available: if the serum B12 level is below 180ng/L (or local laboratory threshold) then staff should make a 15 minute appointment with the GP or nurse who requested the blood test.

Results of other blood tests: many conditions are commonly found alongside Vitamin B12 deficiency, and should be treated in the normal manner at the same time as administering B12 replacement therapy. See also the hypoadrenalism (Addison's disease or adrenal insufficiency) treatment protocol.

Confirming B12 deficiency

Blood tests are categorised as follows when combined with signs and symptoms indicative of B12 deficiency.

Table A1-1 Confirming B12 deficiency

Blood serum B12 ng/L	B12 nmol/ml	classification
Less than 200 ng/L	< 148 nmol/ml	Clinically significant/ severe B12 deficiency
200-350 ng/L	148 – 259 nmol/ml	Moderate deficiency
>350 ng/L	> 259 nmol/L	"Subtle" (subnormal/low normal blood serum B12 but with signs & symptoms)

This information is based on BMJ Best Practice 2012 and Harrison's Internal Medicine (starting with 16th Edition 2004)

In addition to these classifications, patients can be assigned to a therapeutic trial (to confirm a suspected diagnosis) or prophylaxis (where the clinician has evidence to suggest this is needed to prevent symptoms developing or getting worse). For example, if the patient is diagnosed as moderate or subtle deficiency (>180ng/L or >200ng/L with signs and symptoms, other autoimmune condition or family history) then they should be clinically reviewed every 4 weeks until you reach a clinical decision whether to commence

treatment – even when the B12 level does not drop below 180-200ng/L. A deterioration of condition demonstrated by signs and symptoms is sufficient to commence a **therapeutic trial**.

Prophylaxis of vitamin B12 deficiency

In the following instances B12 replacement therapy should be instituted as a prophylactic measure (to prevent further deterioration or even development of symptoms) regardless of blood serum B12 concentration: Prophylaxis is expected to continue for life.

1- **Specific medical history** renal imbalance, diabetes, >65 years old, or following GI surgery, Crohn's colitis, early onset dementia

2- **Moderate/ subtle B12 deficiency with mild signs & symptoms**

3- **Moderate/ subtle B12 deficiency with severe signs & symptoms:** patient presenting with strong family history, presence of other auto-immune conditions, major signs and symptoms which could become irreversible if treatment is not commenced urgently eg optic neuritis/ neuropathy, sudden onset blindness, subacute combined degeneration, ME, CFS, MS-like presentation, single limb paralysis, sudden loss of muscle mass (Motor Neurone Disease-like presentation), non-epileptic seizures, dysphagia, Bell's Palsy/ Ramsey Hunt syndrome, Parkinson's like presentation, dementia, total alopecia, migrainous headache, temporal arteritis, recurrent miscarriages, dysfunctional uterine bleeding, or psychosis

Other Actions to Take

- If clinical depression is suspected – complete PHQ9 and treat/refer as appropriate
- Neurological manifestation – neurological examination and refer to neurologist for further investigation
- Provisional diagnosis of any other condition – refer to appropriate speciality.

Mother & Foetus, Neonate, Child - B12 deficiency: prevention, early diagnosis and treatment

An undiagnosed, untreated B12 deficient mother receiving only folic acid supplement could deliver her child with neuromuscular damage, sub-acute combined degeneration of the spinal cord, congenital abnormalities, tumours including brain damage and spina bifida. This can be avoided with B12 replacement before and during pregnancy (treat as for B12 deficiency (PA[40]) with neurological signs and symptoms).

The neonate 0 – 1 month born to an untreated B12 deficient mother should receive intensive IV B12 replacement treatment in the hospital neonatal department. Folate deficiency frequently accompanies B12 deficiency and folate may be offered in combination.

See treatment for B12 deficiency (PA) with neurological signs & symptoms.

Child 1 month – 13 years

If an untreated B12 deficient mother opts to breast feed, mother and infant will require B12 replacement and regular monitoring as per BNF guidelines. Please note, baby milk powder fortified with vitamin B12 may not be sufficient to correct the moderate to severe deficiency in a new-born.

A child, whether born to a known B12 deficient mother or not, who presents with delayed development, hyper activity, behavioural problems, dyspraxia, learning disability, autistic spectrum disorder like presentation, should initially be screened by blood test, to exclude B12 deficiency, underactive thyroid, inborn errors of metabolism, and any other condition suspected.

[40] PA – Pernicious Anaemia

Treatment as per BNF guidelines for children. Review the signs and symptoms and vary the frequency according to the child's needs (following the loading doses of alternate day injections); 1mg weekly, fortnightly, monthly, 2 monthly or 3 monthly.

When required, refer to appropriate paediatric speciality.

Deciding how to treat B12 deficiency

B12 deficiency is a multi-system, poly-glandular, multi-point poisonous syndrome. In the past, macrocytosis and anaemia were common indicators of B12 deficiency and the disease is variously called Megaloblastic anaemia, Pernicious Anaemia (PA), and macrocytic anaemia. However with folate fortification of food stuffs, haematological effects of vitamin B12 deficiency are masked and B12 deficiency is most likely to manifest with neuropathy symptoms or neuropsychiatric symptoms, due to severe neurological damage.

Before treatment starts, patients should agree to B12 replacement therapy by signing and dating the appropriate consent form.

Where 1-3 body systems are affected (see Appendix A – symptoms) and blood serum B12 is below the local lab threshold (200ng/L usually) then treat as for B12 deficiency (PA) without neurological involvement.

Where 1-3 body systems are affected and blood serum is above the local lab threshold, then monitor the patient and review. Following specific medical history, prophylaxis may be initiated.

4-6 body systems affected, blood serum more than 350ng/L (subtle deficiency) then offer a therapeutic trial to confirm diagnosis. Blood serum less than 350ng/L (moderate and severe deficiency), follow treatment for B12 deficiency (PA) with neurological signs & symptoms.

If more than 6 body systems are affected, commence treatment immediately without waiting for blood tests. Treat as B12 deficiency (PA) with neurological signs & symptoms.

Treatment regimes:

B12 deficiency (PA) and other macrocytic anaemias without neurological involvement. A small number of people have B12 deficiency and do not exhibit neurological signs and symptoms: hydroxocobalamin[41] by intramuscular injection Initially 1mg 3 times a week for 2 weeks then 1mg every 2-3 months. *Clinically review every 3 months with or without serum B12 test and if clinically indicated increase the frequency according to patient's clinical requirements (to minimise symptoms)

B12 deficiency (PA) without macrocytosis with neurological signs and symptoms. Initially hydroxocobalamin (or methylcobalamin) 1mg on alternate days until no further improvement (maximum reversal of neuro-psychiatric signs and symptoms are achieved), then 1mg every 1 or 2 months. *Clinically review every 2 months with or without serum B12 and if clinically indicated increase the frequency to every month or more frequently

Note: treatment should be tailored to patient need; some people need injections more frequently than once per month for short periods.

Prophylaxis of B12 deficiency for specific medical history and patients presenting with moderate or severe symptoms but may not have low blood serum B12 ('subtle' B12 deficiency): 1mg hydroxocobalamin or

[41] methylcobalamin is used in USA, Canada, India, Japan and other countries. Pharmacists in Wales also report that they can prescribe methylcobalamin. Methylcobalamin is considered superior to hydroxocobalamin by many people because it is one of the natural body forms of B12

methylcobalamin IM or SC alternate days for 6 doses (2 weeks), then 1mg IM or SC every 1-2 months: review and increase frequency to minimise the development of symptoms

Oral B12 treatment may also be offered for mild deficiency, and where a B12 deficiency has been demonstrated through a therapeutic trial but absorption of B12 from the gut is normal (ie no autoimmune conditions, no GI tract surgery or disorders, no IF or parietal cell antibodies) and dietary deficiency is suspected (vegetarian or vegan, or limited intake of red meat). Oral (OC[42]) B12 1mg/ 3mg/ 5mg per day. The patient's blood serum B12 should rise rapidly. If the patient's signs and symptoms do not improve then review and consider treatment for B12 deficiency (PA) without neurological signs.

Therapeutic Trial should be used where B12 deficiency is suspected because of signs and symptoms, but B12 deficiency is subtle or subclinical on the basis of blood serum results. 1mg IM or SC (hydroxocobalamin or methylcobalamin) should be given alternate days for 2 – 3 weeks (6 to 9 doses) followed by 1mg IM or SC[43] per week for 3 months. Signs and symptoms should be monitored, and frequency varied if required. If there is no improvement in signs and symptoms after 3 months (13 weeks) then B12 deficiency can be excluded. A therapeutic trial will not interact with other medication given and other treatment can be started at the same time.

Cyanide poisoning (victims of smoke inhalation who show signs of significant cyanide poisoning) hydroxocobalamin (or methylcobalamin in some countries) the usual dose is 5g (or 70mg/kg in children) by intravenous infusion, given once or twice according to severity.

NOTE THAT cyanocobalamin is licensed for 1mg IM injection monthly; because of reduced retention in the body in comparison to hydroxocobalamin and methyl-cobalamin (not licensed). Cyanocobalamin is excreted by the kidney preferentially which is why Cobalamin is used to treat cyanide poisoning. Current guidelines suggest that cyanocobalamin should NOT be used for treating B12 deficiency.

Nitrous oxide anaesthesia. Nitrous oxide inactivates Vitamin B12 in the body including brain cells. Therefore a B12 deficient patient (or his or her GP) should alert the surgeon and anaesthetist so that an alternative anaesthetic agent will be used during surgery. A full blown megaloblastic state can develop over the course of just a few days following nitrous oxide anaesthesia.

Cessation of treatment

In most cases, treatment should continue for life. Treatment should be varied as follows:

- If the patient shows signs of improvement or is stable for 2 years, then the frequency of injections can be extended from monthly to every 2 months.
- If the patient suffers symptoms before the next scheduled injection, then the GP should consider injections closer together to minimise suffering
- Blood serum B12 is not considered a good measure of the effectiveness of injections; relief from signs and symptoms is the best measure. It should be noted that the majority of B12 in blood serum is in the inactive form, and that the serum B12 test measures all forms of Cobalamin including the less biologically active cyanocobalamin form.

[42] OC – Over the Counter. B12 can be purchased as oral lozenges or spray from health food shops and the internet. Use methylcobalamin for preference

[43] Injections Intra-Muscular (IM, into the muscle of the shoulder or thigh) or Sub Cutaneous (SC, stomach, buttock etc). IM injections will be released into the blood more quickly giving faster effects but lasting less time, whereas injections into fatty tissue will be released more gradually

One Minute Health Check – B12 Deficiency signs and symptoms

A quick score will reveal if B12 deficiency, underactive thyroid or iron deficiency anaemia are 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? 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.

Table A1-2 One Minute Health Check symptoms

	Signs and Symptoms	Score 1-10
	Energy/ haemopoetic	
	Weariness, Lethargy, tiredness, fatigue, faints	
	Sleepy, tired in the afternoon	
	Nervous system	
	Tremor, foot drop	
¥	Loss of balance (ataxia), seizures, falls	
¥	Tingling or numbness in hands and/or feet, burning sensation	
	Restless leg syndrome	
	Facial Palsy	
	Spastic movements, Crampy pain in limbs	
¥	Stiffness of limbs, muscle wasting	
¥	Weakness or loss of sensation in limbs, shooting pain in back/ limbs, paralysis	
	Migrainous headache	
	Psychiatric	
	Irritable, snappy, disturbed sleep	
	Confused, Memory disturbance/ forgetful, fogginess	
	Tension Headaches	
*	Mental slowness, Mood swings, Anxiety/ Panic Attacks, depression	
*	Psychosis, hallucinations, delusion	
	Eye Ear Throat	
	Blurred vision/ double vision/ drooping of eyelid (lid lag), orbital pain	
	Dizziness, tinnitus	
	Difficulty swallowing, persistent cough	
	Immune System	
	Prone to recurrent URTI, UTI, Respiratory infections	
	Other auto-immune conditions	
	Hypoadrenalism, myxodema/ underactive thyroid	

Signs and Symptoms	Score 1-10
Cardiovascular/ Respiratory	
Shortness of breath, wheeziness	
Palpitations, chest pain	
Pallor, lemon yellow complexion	
Bruising, Vasculitis	
Gastro-Intestinal (GI)	
Sore tongue, bleeding gums	
Red beefy tongue	
Cracking the angles of mouth	
Metallic taste, unusual taste,loss of appetite,loss of weight	
Gastric symptoms-acidity, heartburn	
Intermittent diarrhoea, IBS	
Skin hair nail skeletal	
Premature greying	
Alopecia, Unexplained hair loss	
Joint inflammation, swelling, pain	
Dry skin, brittle nails	
Genito-Urinary (GU)	
Heavy painful periods, irregular periods, infertility & frequent miscarriages	
Polycystic ovarian disease	
Loss of libido	
Shooting pain from groin to perineum	
Incontinence	
Personal & Family History	
Family history of B12 deficiency (Pernicious Anaemia), underactive thyroid, diabetes, vitiligo, depression	
Vegetarian, vegan, poor diet	
Alcoholism, Smoking	

* PHQ9 Patient Health Questionnaire to be completed
¥ Neurological examination and appropriate referral if indicated

Physician should also order routine blood tests including serum B12 in the following cases:

- ME, CFS, Fibromyalgia, Hypoadrenalism, MS-like presentation
- Children born to B12-deficient mothers, presenting with behavioural problems, learning disability, dyspraxia,dyslexia and autistic spectrum disorders

Before making a provisional diagnosis of B12 deficiency, exclude all other possible diagnoses, with appropriate additional blood tests as clinically indicated.

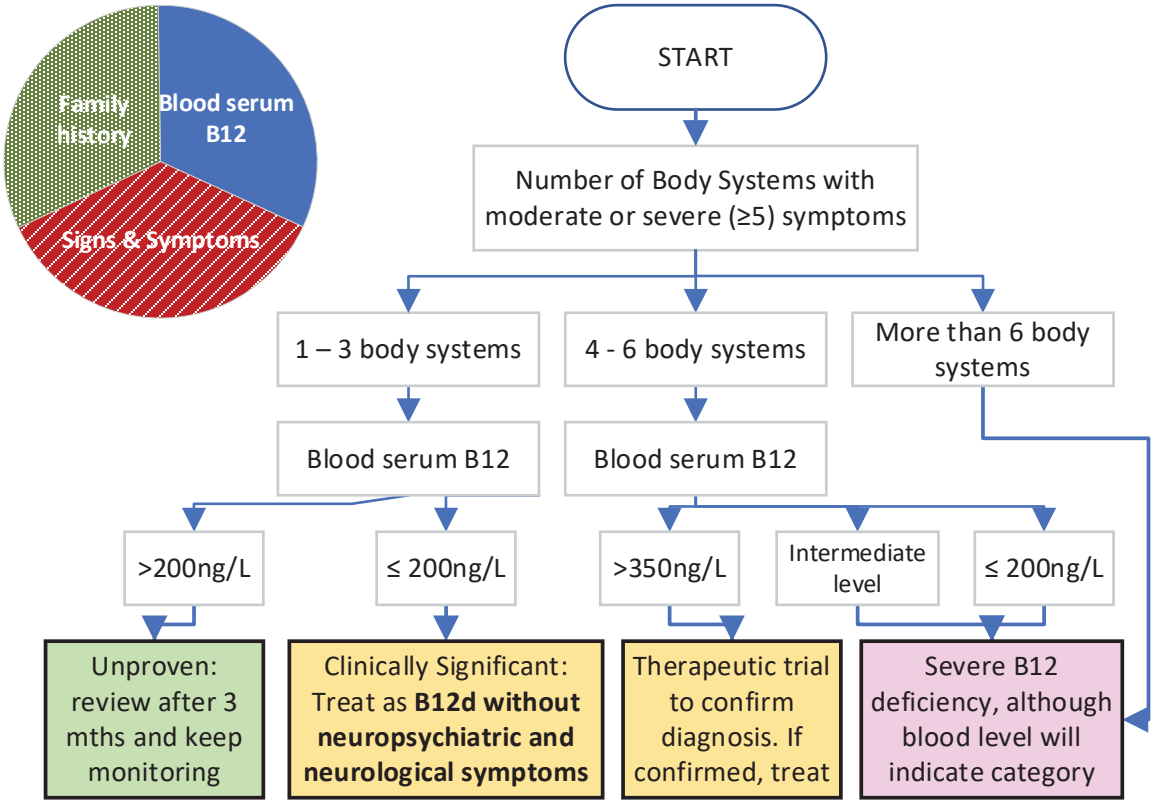
Decision Tree to diagnose / exclude B12 deficiency

Record the MAXIMUM score of any single symptom within a body system, in the yellow header bar of the body system (on the Signs and Symptoms form on page 271).

Count scores of severity 5 or above in the yellow Signs and Symptoms bars (ie count body systems).

1. **B12 deficiency (Pernicious Anaemia) and other macrocytic anaemias without neurological involvement**[44]. Hydroxocobalamin or methylcobalamin initially 1mg 3 times per week for 2 weeks, then 1mg every 2 – 3 months

2. **B12 deficiency (Pernicious Anaemia) with neurological signs and symptoms**[44]. Initially 1mg on alternate days until no further improvement (maximum reversal of neuro-psychiatric signs and symptoms are achieved), then 1mg every 1 – 2 months.



3. **Prophylaxis or Therapeutic Trial**. 1mg IM or SC (hydroxocobalamin or methylcobalamin) should be given alternate days for 2 – 3 weeks (6 to 9 doses) followed by 1mg IM or SC[45] per week for 3 months. If there is no improvement in signs and symptoms after 3 months (13 weeks) then B12 deficiency can be excluded. A therapeutic trial will not interact with medication given and any other treatment can be started at the same time. Review treatment pathway after 3 months.

[44] Clinically review every 1 or 2 months with or without serum B12 and if clinically indicated increase the frequency to every 2 months, every month or more frequently

[45] Injections Intra-Muscular (IM, into the muscle of the shoulder or thigh) or Sub Cutaneous (SC, stomach, buttock etc) of hydroxocobalamin or methylcobalamin 1mg/ml or 5mg/ml

B12 Consent Form

Dear patient

Your blood test shows that you have low levels of Vitamin B12 in the body, and your signs and symptoms indicate that you have a deficiency of Vitamin B12.

Vitamin B12 is essential for life. Vitamin B12 deficiency can result in damage to every system and gland in the body

- it is needed to make new cells in the body, including red blood cells, and for enabling genes (DNA) to switch on and off
- it is needed for maintenance of the myelin sheath around nerve cells, and deficiency can result in numbness, paralysis, or shooting pains, as well as confusion and memory loss
- it is a vital catalyst in the body's energy pathways, so without it you may suffer lethargy and tiredness, and at the same time disturbed sleep
- It helps maintain cell membranes, which means it is important for a normal immune system, for hormone production, and for the production of digestive juices.

Vitamin B12 is found in meat, fish, eggs and milk but not in fruit or vegetables. The medical view is that a normal balanced diet contains enough B12. However, failure to absorb Vitamin B12 from food will cause B12 deficiency resulting in many forms of illnesses and disabilities.

Treatment – Vitamin B12 can be administered by either injection or taken by mouth. This is an ongoing treatment and your Doctor will advise you on how this will be given. You will be monitored and have further blood tests, to check on progress.

Risks – Although injectable B12 is completely non-toxic, some people report a little local discomfort after injection.

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:

Diagnosis

Clinically significant B12 def less than 200 (lab threshold) (with signs & symptoms) .....[ ]

Subclinical / subtle B12 Def (above lab threshold) (WITH signs & symptoms) .....[ ]

Additional Requirements

Signs & Symptoms sheet completed.....[ ]

Consent form signed.....[ ]

Patient Information Leaflets given.....[ ]

Vitamin B12 deficiency and direct or indirect causation of disease

Deficiency of vitamin B12 is a multi-system, polyglandular, multipoint poisonous syndrome. B12 is required for proper function of most of the body's systems, so deficiency leads to disease in these systems.

This appendix lists some of the common conditions that can be treated successfully by using Vitamin B12 replacement therapy, and a causative mechanism can be described.

Haematological

Unexplained recurrent anaemia
Myelodysplasia
Pancytopaenia / bruising

Psychiatric

Depression
Memory loss / confusion
Anxiety
Psychosis
Angry / moody / snappy

Gastro-intestinal

Recurrent gastritis
Mouth ulcers, bleeding gums
Pernicious anaemia
IBS / diverticulosis
Unexplained diarrhoea
Crohn's Colitis

Cardio-Vascular / Respiratory Systems

Cardiac failure – arthrosclerosis, stroke
Temporal arteritis
Vasculitis
Exacerbation of angina – palpitations, breathlessness
Asthma exacerbation

ENT (Ear, nose & throat)

Tinnitus / vertigo
Glossopharyngeal neuropathy (swallowing difficulties)
Persistent cough
Dizziness / falls

Endocrine / Immune systems

Post Viral Immune Deficiency Fatigue Syndrome (ME)
Poor wound healing/ susceptibility to infection
Auto-immune conditions such as vitiligo, myxodema, hypoadrenal diabetes coexisting with B12 deficiency

Neurological

Dementia
Alzheimers'
Optic Atrophy / blindness
Doublevision, Ptosis
Loss of sensation in limbs, trunk, face, genitalia
Pseudo seizures, non-epileptic seizures
Blackouts and faints
SubAcute Combined Degeneration (SACD)
Single limb paralysis
Multiple-sclerosis like B12 deficiency syndrome
Neuropathic pain / myopathy
Cramps / crampy pain
Babies with neuromuscular damage may be born to mothers who are B12 deficient during pregnancy
Tension / migraine headaches
Parkinson's like presentation
Motorneurone like presentation with limb muscle atrophy
Bell's palsy
Ramsay Hunt syndrome

Bone

Osteoporosis, suppressed activity of osteoblasts
Inflammatory polyarthritis

Dermatology

Alopecia
Dry scaly skin/ dermatitis
Brittle nails

Genito-Urinary

Dysfunctional Uterine Bleeding
Repeated miscarriages
Polycystic ovarian disease
Dysmenorrhoea, menorrhagia
Recurrent UTI
Loss of libido
Double-incontinence

If treatment is delayed, this may cause irreversible damage, or fatality. Always exclude vitamin B12 deficiency before making a final diagnosis and deciding treatment options.

If vitamin B12 deficiency co-exists with other causes, B12 therapy compliments other treatments rather than interferes

Exclusion Criteria

Conditions which, if diagnosed, will exclude a diagnosis of B12 deficiency unless the patient meets above criteria for diagnosis:

- Depressive illness
- Phobic anxiety state
- Neurosis
- Bulimia
- Anorexic nervosa
- Vasovagal attacks
- Partial seizure
- Epileptic seizure
- Brain tumour
- Cranio pharyngeoma
- Temporal arteritis
- Gastric colon and renal cancers
- Cerebral aneurism

Appendix 2 Protocol for Diagnosing Hypoadrenalism/Addison's Disease

Relevance

This protocol is relevant to all diagnosing clinicians, i.e. 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 corticotropic 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, myxodema etc.

Symptoms to consider when making a diagnosis are listed in the table on page 282. The table 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.

The most important/ frequent symptoms are:

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

Table A2-1 Diagnosis using results of symptoms table – 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 mol/L

Stage 1 hypoadrenalism: Pre clinical

8-9 AM cortisol 400-500nmols/L ≈20% adrenal cortical damage[46]	a) Signs and Symptoms mild. b) Patient has a history of vitamin B12 deficiency and/or presence of other autoimmune polyendocrine conditions (APS). c) Family history of vitamin B12 deficiency and presence of other autoimmune 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 (myxoedema, vitamin 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	a) Signs and Symptoms mild to moderate b) Patient has a history of vitamin B12 deficiency and/or presence of other autoimmune polyendocrine conditions (APS). c) Family history of vitamin B12 deficiency and presence of other autoimmune 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.

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

Clinically follow up with 8-9 am 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.

- Continue to treat appropriately or adequately other co-existing autoimmune conditions (hypo/hyper thyroidism, vitamin 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	a) Signs and Symptoms moderate. b) Patient has a history of vitamin B12 deficiency and/or presence of other autoimmune p9lyendocrine disorders (APS). c) Strong family history of vitamin B12 deficiency and presence of other autoimmune conditions.
ACTH - low/normal/high Aldosterone – normal/low DHEA – low/normal	

Treatment

Appropriate replacement treatment prescribed. Repeat bloods and 8-9 am 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.

Table A2-2 Stage 3 dose of hydrocortisone

	7 am	12 noon	5 pm
Hydrocortisone	10mg	10mg	5mg
OR Prednisolone	2mg/3mg	2mg/3mg	1mg

Hydrocortisone is the generally preferred replacement treatment. 1mg of Prednisolone is equivalent to 4mg of Hydrocortisone.
Hydrocortisone - Peak blood level in 3 hours. Prednisolone has a longer half-life.

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. As it is 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.

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.

Treatment

Refer to Endocrinologist under 2-week rule.

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

Table A2-3 Stage 5 dose of hydrocortisone

	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)

8-9 AM cortisol 0-25 nmols/L ≈80-95% cortical damage	Signs and symptoms: • patient collapse, semiconscious/unconscious; • unable to self-inject emergency hydrocortisone; • patient critically ill.

Treatment

Administer 100 mg 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.

Table A2-4 Stage 6 dose of hydrocortisone

	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.

Hypoadrenalism (Addison's Disease) signs and symptoms - check

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)
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

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