

Investigation and Management of vitamin B12 deficiency in Primary Care for adult patients

Target audience

This document is for health care professionals who will be diagnosing and prescribing vitamin B12 in primary care in South-West London.

Summary

- The most common cause of severe vitamin B12 deficiency in the UK is pernicious anaemia.
- Treatment of vitamin B12 deficiency is the only indication for prescribing of hydroxocobalamin or cyanocobalamin in primary care. It should not be prescribed for chronic fatigue syndrome or myalgic encephalopathy.
- There is no gold standard test to define vitamin B12 deficiency. A vitamin B12 blood test is not 100% reliable as it may miss 5% of the true disease.
- A serum cobalamin level less than 200nanogram/litre (ng/L) is appropriate in most cases to diagnose deficiency.
- Intramuscular (IM) hydroxocobalamin is recommended for the initial treatment of vitamin B12 deficiency.
- Diet assessment and advice are essential as dietary deficiency can usually be easily corrected.

Causes of vitamin B12 deficiency

Prevalence of vitamin B12 deficiency is around 6% in people less than 60 years, 20% in those aged more than 60 years and 11 % in people who follow vegan diets.

Pernicious anaemia is an autoimmune condition that results in destruction of gastric parietal cells. These cells produce intrinsic factor. It is the most common cause of severe vitamin B12 deficiency in the UK and mainly affects those over 70 years of age. It can take many years for vitamin B12 deficiency to develop due to a small daily requirement (1-2 microgram/day) and large stores of vitamin B12 in the liver.

Other causes of vitamin B12 deficiency are rare, but include:

- Malabsorption due to gastrectomy, gastric resection, crohn's disease, chronic alcoholism, coeliac disease, pancreatic failure and/or chronic alcoholism.
- Nutritional such as inadequate dietary intake of vitamin B12 (e.g., strict vegan diet) and malnutrition.
- Medication such as colchicine, metformin or prolonged use of a proton pump inhibitor. Contraceptive pills can also cause a deficiency, this is thought to be related to a reduction in the vitamin B12- carrying protein (transcobalamin).
- Other: pregnancy and lactation (low cobalamin levels found in the third trimester may be physiological) genetic disorders and infection. Individuals with Down's Syndrome may also be deficient in vitamin B12 and benefit from supplementation.

Indications for measuring serum vitamin B12 levels

Routine testing of vitamin B12 should not be undertaken. If a vitamin B12 test is required in patients with suspected vitamin B12 deficiency, then two blood tests must be requested. One to measure cobalamin levels and the other for Anti-Intrinsic factor antibody (Anti-IFAB) to confirm the presence of pernicious anaemia.

Signs and Symptoms of vitamin B12 deficiency

Vitamin B12 deficiency affects multiple systems. Signs and symptoms depend on the severity of depletion, ranging from anaemia and fatigue to bone marrow suppression and impaired cognition. The onset of anaemia can develop gradually over many years and symptoms may not appear until it is severe. It is important to note that clinical features of vitamin B12 deficiency can occur without anaemia and without low serum levels of vitamin B12.

Signs and symptoms suggestive that vitamin B12 levels should be tested are listed below.

Haematological

- Isolated red cell macrocytosis
- Macrocytic anaemia (especially if MCV more than 110fl)
- Pancytopenia (especially if MCV more than 120fl)

Neurological or Psychiatric

- Optic neuropathy
- Peripheral neuropathy (sensory or motor)
- Symmetrical neuropathy affecting the legs more than the arms. This usually presents with ataxia or paraesthesia
- Subacute combined degeneration of the cord

Psychiatric

- Altered mental state such as confusion, memory problems
- Cognitive changes such as dementia
- Loss of mental and physical drive
- Psychiatric disturbances, ranging from mild neurosis to severe dementia

Other

- Angular cheilosis
- Anosmia, glossitis, and loss of taste
- Autonomic complications such as postural hypotension
- Gait problems – consider if history of falls
- Infertility
- Investigation of possible malabsorptive process
- Urinary or faecal incontinence

Interpreting investigation results

Serum cobalamin

- The clinical normal level of serum cobalamin is unclear. It has been suggested that a level below 200ng/L is appropriate to diagnose deficiency in most cases.
- Levels of serum cobalamin are not easily correlated with clinical symptoms.
- Patients with vitamin B12 levels less than 100 ng/L usually have clinical or metabolic evidence of B12 deficiency.
- Women taking oral contraceptives may show decreased cobalamin levels because of a decrease in cobalamin carrier protein, however, this may not result in deficiency.
- Serum cobalamin levels fall in pregnant women and are less reliable in determining deficiency.
- The finding of a low total serum cobalamin level may be further evaluated by testing for anti-IFAB.

Anti-Intrinsic factor antibody (Anti-IFAB)

- Once a patient has been diagnosed with a vitamin B12 deficiency, check for Anti-IFAB and determine if there is an underlying cause such as pernicious anaemia.
- Pernicious anaemia is characteristically diagnosed by the presence of Anti-IFAB.
- Be aware that some patients can have antibody-negative pernicious anaemia but note:
 - Anti-IFAB assess for pernicious anaemia only. There are other causes of B12 deficiency.
 - Around half of patients with pernicious anaemia are anti-intrinsic factor negative. Treatment remains the same.
- A history of other autoimmune diseases such as hypothyroidism and family history increase the pre-test probability of pernicious anaemia.
- All patients with anaemia, neuropathy or glossitis, and suspected of having pernicious anaemia, should be tested for anti-IFAB regardless of cobalamin levels.
- Patients found to have a low serum cobalamin level in the absence of anaemia and who do not have food malabsorption or other causes of deficiency, should be tested for IFAB to clarify whether they have an early or latent presentation of pernicious anaemia.

Treatment of vitamin B12 anaemia (pernicious anaemia or other macrocytic anaemias)

Hydroxocobalamin has completely replaced cyanocobalamin as the form of vitamin B12 of choice for therapy; it is retained in the body longer than cyanocobalamin and

for maintenance therapy can be given at intervals of up to three months. *Cyanocobalamin* solution and *Cytamer*[®] injections are not prescribable in NHS primary care.

For patients with neurological involvement

Seek urgent advice from a haematologist. If specialist advice is not immediately available, consider the following:

- **Initial treatment:** IM hydroxocobalamin 1 mg once daily on alternate days until no further improvement. Review after 3 weeks.
- **Maintenance treatment:** IM hydroxocobalamin 1 mg every 2 months for life.

For patients with no neurological involvement

- **Initial treatment:** IM hydroxocobalamin 1 mg 3 times a week for 2 weeks.
- **Maintenance treatment:** Dependant on whether the deficiency is diet related or not.
 - Not thought to be diet related: IM hydroxocobalamin 1 mg every 2- 3 months for life.
 - Thought to be diet related
 - Cyanocobalamin tablets 50–150 micrograms daily between meals (see 'self-care' section below)
 - or**
 - Twice-yearly hydroxocobalamin 1 mg injections.

Injections may be preferred:

- In the elderly (who are more likely to have malabsorption)
- In vegans (current available brands of oral cyanocobalamin may not be suitable).

In vegans' treatment may need to be life long, whereas in others treatment may be stopped once vitamin B12 levels have been corrected and the diet improved.

Effective vitamin B12 replacement should correct a macrocytic anaemia within 2 months and improve or correct neurological signs and symptoms within 6 months.

Potential side-effects of vitamin B12

Vitamin B12 is usually well tolerated, however some patients may experience side effects such as diarrhoea; dizziness; headache; hot flush; nausea; skin reactions and urine discolouration. This is not an exhaustive list of side effects.

It is worth noting the following regarding cyanocobalamin treatment

- Orally administered cyanocobalamin is absorbed passively in the duodenum and small intestines even without the presence of intrinsic factor. The degree of absorption is dose-dependent and is about 1% of a dose of 1 mg.

- This dose is sufficient for the maintenance treatment of patients with pernicious anaemia and other forms of malabsorption of vitamin B12.
- Oral therapy with higher doses can be given initially, but in cases of manifest B12 deficiency, parenteral therapy should be preferred for faster remission and liver repletion.

Self-care

NHS England has released guidance on [Conditions for Which OTC Medications Should Not Routinely be Prescribed](#). Further information for clinicians can also be found on the [SWL website](#), [Information for Patients](#), [Position Statement on the prescribing of vitamins and minerals](#).

There may be instances where patients are unable to purchase oral cyanocobalamin such as those with reduced mobility, in care homes and those visiting homes restricted by Covid outbreaks / family infection. In these instances, it is at the discretion of the prescriber as to whether cyanocobalamin is prescribed on a FP10 prescription.

Dietary sources of vitamin B12 include

- Eggs
- Foods fortified with vitamin B12. Examples include breakfast cereals, some soy products and breads. These are good alternative sources to meat, eggs and dairy products.
- Meat
- Milk and other dairy products
- Fish especially oily fish such as sardines, herrings, salmon, mackerel

Further information about dietary recommendations can be found at the following website, The [Eatwell Guide](#).

Monitoring

The following is a summary of monitoring requirements once treatment with vitamin B12 has commenced:

- Cobalamin (vitamin B12 level): On-going monitoring of vitamin B12 levels is unnecessary as results are unhelpful. Vitamin B12 levels increase with treatment regardless of how effective it is. Retesting is not usually required; however, levels can be measured 1 to 2 months after starting treatment if there is no response, or lack of compliance with treatment is suspected.
- Full blood and reticulocyte count: Within 7 to 10 days of starting treatment and then after 8 weeks of treatment
- Iron and folate level (if not done already): After 8 weeks of treatment
- Neurological symptoms: Improvement begins within one week and complete resolution usually occurs between six weeks and three months.

Referral to endoscopy for pernicious anaemia

- Individuals with pernicious anaemia have a higher risk of gastric cancers.
- The British Society of Gastroenterology says a baseline endoscopy should be considered for ALL ≥ 50 y with laboratory-confirmed pernicious anaemia (B12 deficiency and positive antibodies).
- If someone with known pernicious anaemia develops an iron deficiency anaemia, this should be investigated with endoscopy.
- Surveillance endoscopy is not currently recommended.

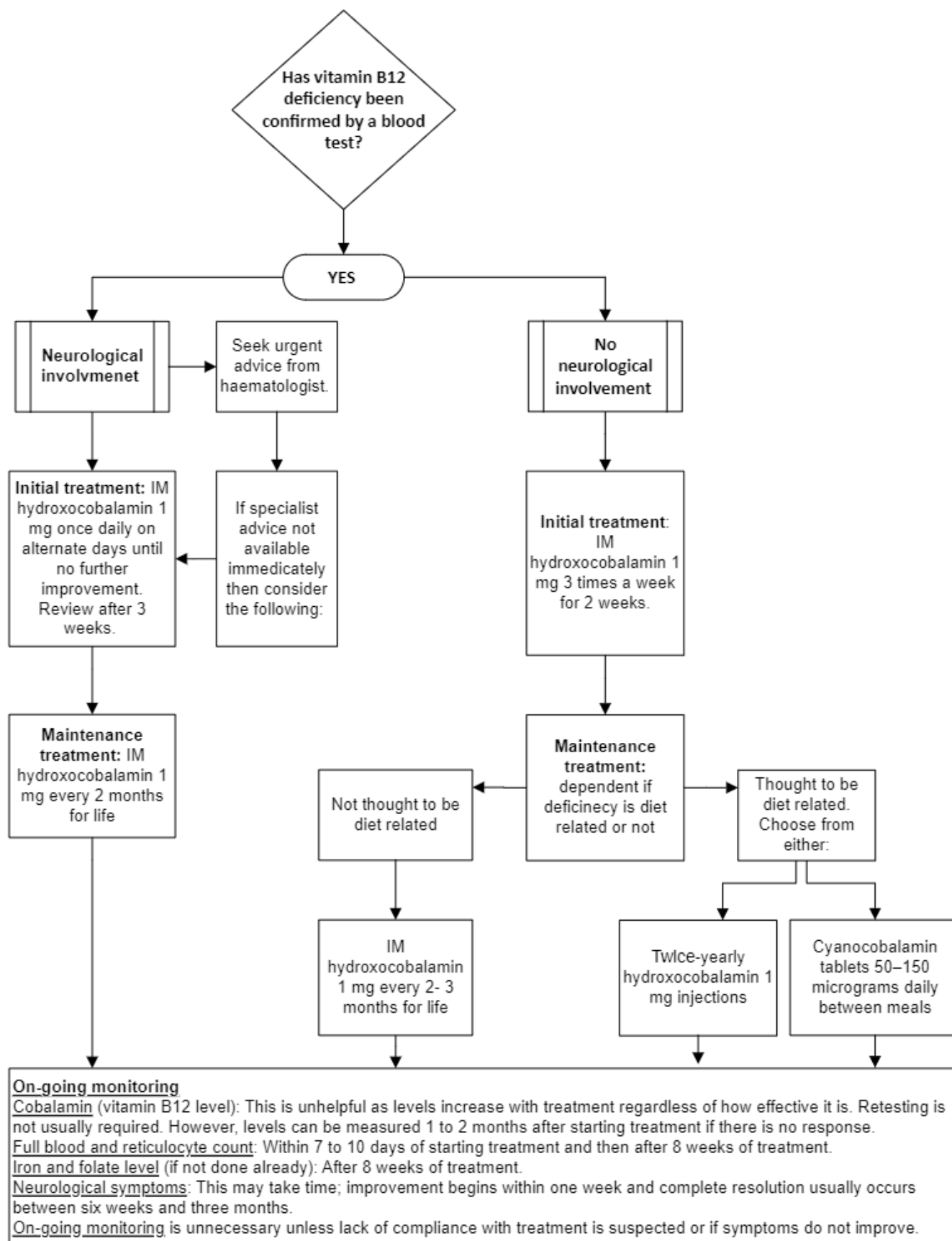
Refer to a haematologist

- If a diagnosis is uncertain or unclear.
- If the cause of B12 deficiency unclear.
- If the response to treatment is inadequate.
- If the patient is pregnant or neurological symptoms are present.
- If the suspected cause is haematological malignancy or another blood disorder.
- If the mean cell volume is persistently more than 105 fl.
- Refer to a gastroenterologist for malabsorption or inflammatory bowel disorder.
- Suspected gastric malignancy with anaemia secondary to gastrointestinal blood loss.

Refer to a dietician

- If vitamin B12 or folate deficiency is thought to be due to a poor diet.

Investigation and treatment of adult patients presenting with signs or symptoms of vitamin B12 deficiency in primary care



References and resources

- Clinical Knowledge Summaries. [Anaemia - B12 and folate deficiency](#). Last revised July 2020.
- Devalia, V., Hamilton, M. and Molloy, A., 2022. [Guidelines for the diagnosis and treatment of cobalamin and folate disorders](#). [online] BJHaem.
- [British National Formulary](#).
- Summary of product characteristics: [Orobalin 1 mg film-coated tablets](#). Last updated 24th May 2021.

Document History

Version: V 1.0

Author: **SWL ICB**

Approved by: Integrated medicines committee (IMOC)

Approval date: **16/11/2022**

Review Date: 2 years from approval date or sooner where appropriate.

Version V1.1: Minor formatting for accessibility (1/12/2022)