

Investigation and treatment of Vitamin B12 (cobalamin) deficiency in Adults (Please see notes on page 3 for information about children)

When to check vitamin B12 levels:

- Macrocytosis (MCV>100fl)
- Previous gastric surgery/inflammatory bowel disease/Coeliac
- Cytopenias (eg isolated neutropenia, thrombocytopenia, anaemia or pancytopenia)
- Neuropsychiatric symptoms or peripheral neuropathy where the cause is not known
- Glossitis
- Iron deficiency anaemia not responding to adequate oral iron

Algorithm 1: Serum cobalamin <150 mcg or serum cobalamin 150-250 ng/ml and neurological/neuropsychiatric symptoms with no other identifiable cause or strong clinical suspicion of deficiency (eg SACD) at any B12 level
Check folate level but replace B12 first if deficient.
Modify any risk factors before proceeding.

Algorithm 2: No neurological/ neuropsychiatric symptoms and cobalamin 150-250 ng/ml)
Check folate level but replace B12 first if deficient.
Modify any risk factors before proceeding.

Check IFAB levels. NB IFAB can give false positive results if B12 has been given recently, so should be checked prior to starting B12 *Start cobalamin as per "Initial Treatment" box below*

Offer dietary advice; patient may purchase OTC cyanocobalamin 50-100 micrograms OD. Patients should be told to report immediately if weakness or neuropathy develop.

Serum cobalamin in normal range: No further investigation

Repeat serum cobalamin after 3 months

Anti-IFAB positive:
Lifelong treatment as pernicious anaemia with neurological symptoms.

Anti-IFAB negative:
If clinical response present, lifelong treatment as antibody-negative pernicious anaemia. If no response – refer for further investigation

Abbreviations: Anti-IFAB: Anti-Intrinsic Factor Antibody
SACD Subacute combined degeneration of the cord

Persistent reduced serum cobalamin (150-250ng/l)

Anti-IFAB positive: treat as for pernicious anaemia

Check IFAB levels. NB IFAB can give false positive results if B12 has been given recently, so should be checked prior to starting B12.

Anti-IFAB negative

Continue with dietary control +/- OTC cyanocobalamin. Patients should be told to report immediately if weakness or neuropathy develop. If so, treat as pernicious anaemia. Repeat serum cobalamin after 3-4 months

Maintenance treatment in patients with neurological symptoms:
IM hydroxocobalamin 1000 micrograms every 2-3 months for life. No further testing of B12 necessary. **Oral cyanocobalamin is NOT recommended**

Initial Treatment
With Neurological Symptoms present:
IM hydroxocobalamin 1000 micrograms alternate days until no more improvement (review after 3/52).
Without Neurological Symptoms:
IM hydroxocobalamin 1000 micrograms 3 x/wk for 2 weeks.

Maintenance treatment in patients without neurological symptoms & underlying cause not dietary: IM hydroxocobalamin 1000 micrograms every 3 months for life. No further testing of B12 levels is necessary.
Oral cyanocobalamin is NOT recommended

Maintenance treatment if dietary cause:
Dietary advice
Oral cyanocobalamin 50-150 micrograms daily to be purchased over the counter

Causes of vitamin B12 deficiency:

Pernicious anaemia - commonest cause;
Other causes include:

- Drugs e.g. metformin, colchicine, cholestyramine, slow K, neomycin or anticonvulsants.
- Long-term use of H2 receptor antagonists & PPIs can worsen deficiency.
- Inadequate dietary intake (e.g. vegan)
- Chronic alcoholism
- Gastric causes e.g. gastrectomy, gastric resection, atrophic gastritis, *H. Pylori* infection, gastric bypass, congenital intrinsic factor deficiency or abnormality
- Intestinal causes (e.g. malabsorption, ileal resection, Crohn's disease affecting the ileum, chronic tropical sprue, HIV or radiotherapy to the cervix.
- Women on OCP may show decreased B12 levels due to decreased cobalamin carrier protein, rather than a deficiency state
- B12 levels may be falsely low in pregnant women because of the increased plasma volume rather than actual deficiency, which makes it very difficult to diagnose in pregnancy. A pregnant woman with suspected severe B12 deficiency should be started on IM Vit B12 and her Hb monitored. For further information about B12 deficiency in pregnancy see: <https://www.sps.nhs.uk/articles/how-should-severe-vitamin-b12-deficiency-in-pregnancy-be-managed>

Test results:

The clinical picture is the most important factor in assessing the results of the serum vitamin B12. Definitive cut off points for clinical and subclinical deficiency are not possible. Bear in mind the test measures total, not metabolically active vitamin B12. Levels are not easily correlated with clinical symptoms, although patients with vitamin B12 levels <100ng/L almost always have clinical or metabolic evidence of vitamin B12 deficiency, and <150ng/l usually do. In most patients with clinically significant vitamin B12 deficiency, the serum level is below 200ng/L but clinically significant vitamin B12 deficiency may be present even when levels are in the normal range, especially in elderly patients. About 50% with pernicious anaemia will have Anti-Intrinsic Factor Antibody (Anti-IFAB). If Anti-IFAB is present, pernicious anaemia is very likely, but its absence does not rule out a diagnosis of pernicious anaemia. A high MCV is usual in B12 deficiency (but not universal) and hypersegmented neutrophils on a blood film can also be a sign.

What are the signs of B12 deficiency?

Haematological

- Isolated red cell macrocytosis (esp if MCV>110fl); Cytopenias (eg isolated neutropenia, thrombocytopenia, anaemia or pancytopenias)

Seek urgent advice from a haematologist if functional B12 deficiency is suspected i.e. strong clinical features of B12 deficiency e.g. megaloblastic anaemia or subacute combined degeneration of the cord, despite normal vitamin B12

Neurological or neuropsychiatric

SACD, Peripheral neuropathy, Cognitive change e.g. dementia, Optic neuritis; Seek urgent advice from a neurologist

Gastrointestinal

If malabsorption is suspected or if there is a suspicion of gastric cancer or coeliac disease; Seek advice from a gastroenterologist. Consider referral to a dietician if B12 deficiency is due to poor diet.

Other (rare): Angular cheilosis, sore beefy red tongue

Assessing response to treatment:

Perform FBC & reticulocytes 10 days following initiation of treatment to ensure patient is responding to the treatment if there were haematological features in their deficiency. Repeat FBC at 8 weeks to ensure normalisation of Hb. Seek haematology advice if persistent abnormalities despite therapy.

Uncomplicated vitamin B12 deficiency does NOT require routine referral for Haematology outpatient assessment

Use of oral cyanocobalamin: Care must be taken if low dose oral cyanocobalamin is used as this risks suboptimal treatment of latent and emerging pernicious anaemia with possible inadequate treatment of neurological features. **Only use where indicated overleaf.**

Special circumstances

Children

- a. Pernicious anaemia is uncommon in children.
- b. Primary causes to consider include gastric causes and dietary insufficiency.
- c. Treatment of dietary deficiency is usually oral supplements. Please refer children with other causes to the hospital rather than starting them on injections.
- d. Re-test in 3 months and if still low, refer to hospital.

In diabetes mellitus on metformin therapy

No definitive advice can be given on the frequency of monitoring serum cobalamin in patients with type II diabetes mellitus on metformin, but it is recommended that serum cobalamin is checked in the presence of strong clinical suspicion of deficiency

If serum cobalamin levels are reduced, patients should have tests for anti-IFAB because the concurrence of pernicious anaemia with diabetes should be considered.

- If positive, the patient should have lifelong treatment with IM cobalamin.
- If negative, the reduced level may be purely as a result of metformin, although underlying AbNeg PA cannot be excluded.

In the absence of neurological symptoms, oral cobalamin may be considered (50microgram daily for 1 month); subsequent monitoring of serum cobalamin after 6 months and then at yearly intervals is suggested. Currently there are no recommendations on prophylactic administration with oral cobalamin in patients taking metformin.

Patients should be informed about dietary intake.

Patients on oral contraception or HRT

Asymptomatic women taking oral contraception or HRT with mildly reduced serum cobalamin (150–200 ng/l) do not require further investigation but should be advised to review their dietary intake of cobalamin-rich foods, and cobalamin supplements maybe considered and can be bought over-the-counter.

Vegans

Vegetarians, particularly strict vegans, should be considered for monitoring of their cobalamin level according to clinical assessment.

Dietary alterations or oral supplementation may be considered according to the clinical situation, particularly during pregnancy and breast-feeding.

People who are vegan should aim to include foods that are fortified with vitamin B12, at least three times a day. If these foods are not consumed in adequate amounts, the Vegan Society recommends a vitamin B12 supplement which can be bought over the counter. Some products may not be suitable for vegans and the patient should be advised about checking labels.

Poor absorption due to gastrointestinal surgery or disease

Patients who have had bariatric surgery should have their cobalamin status monitored and are likely to need cobalamin supplementation via a route depending upon the type of surgery.

Patients with food bound cobalamin malabsorption may benefit from low dose oral replacement.

OTC information: Vitamin B12 is available over the counter from a pharmacy or health food shop.

Foods containing Vitamin B12

The following foods are good sources of vitamin B12: eggs, cheese, milk, meat (e.g. beef, lamb & pork), fish, marmite
Fortified spreads, soya yogurts & yeast extract
Fortified oat, rice and soya milks.

Useful information for patients can be found here:

- o <http://www.nhs.uk/Conditions/Anaemia-vitamin-B12-and-folate-deficiency/Pages/Treatment.aspx>
- o <https://www.vegsoc.org/B12>

Further references:

CKS Anaemia - B12 and folate deficiency (Feb 2019) <https://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!scenario>
BCSH Cobalamin and folate guidelines. Devalia et al 2014: <http://onlinelibrary.wiley.com/doi/10.1111/bjh.12959/full>
BMJ Best Practice Vitamin B12 deficiency June 2018 <https://bestpractice.bmj.com/topics/en-gb/822>

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Date written: June 2021, Review date: June 2024