

Investigation and treatment of Vitamin B12 (cobalamin) deficiency in primary care

Causes of vitamin B12 deficiency:

Pernicious anaemia; commonest cause

Other causes include:

- Drugs e.g. metformin, colchicine, 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 (causing irradiation of the ileum))

It is also important to note that:

- 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. 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/>

RUH Haematology helpline: 07789 928466

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 IFAB. If IFAB is present, pernicious anaemia is very likely, but its absence does not rule out a diagnosis of pernicious anaemia.

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.

Dietary deficiency:

Advise consumption of foods rich in vitamin B12 e.g. some soy products, breakfast cereals, breads, meat, eggs & dairy products.

Useful information for patients:

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

Referral:

Seek urgent advice from a haematologist if:

- The patient is pregnant (not if mild deficiency)
- 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.

Consider seeking urgent advice from a neurologist if:

- Neurological symptoms are present

Refer to a gastroenterologist if:

- Malabsorption is suspected or if there is a suspicion of gastric cancer or coeliac disease

Consider referral to a dietician if B12 deficiency is due to poor diet.

Assessing response to treatment:

If patient has presented with anaemia, perform FBC & reticulocytes 10 days following initiation of treatment if haematological features in their deficiency. Repeat FBC at 8 weeks to ensure normalisation of Hb. Seek haematology advice if persistent abnormalities despite replacement.

References:

CKS Anaemia - B12 and folate deficiency (July 2015)

<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>

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Algorithm 1: Strong suspicion of cobalamin deficiency with objective parameters e.g. anaemia, glossitis, cognitive impairment, paraesthesia. Check serum cobalamin and folate levels.

- Serum cobalamin <150ng/l: Very probable deficiency
- Serum cobalamin 150-200 ng/l: **probable** deficiency
- Serum cobalamin 200-250ng/L: **possible** cobalamin deficiency (i.e. falsely normal cobalamin)

Check IFAB levels.

Start cobalamin as per "initial treatment" box below

IFAB positive:
Lifelong treatment as pernicious anaemia

IFAB negative:
If clinical response present, lifelong treatment as antibody-negative pernicious anaemia. Check TTG (coeliac screen) & if positive or diarrhoea/abdo pain, refer to gastroenterology.

Algorithm 2: Patient with non-specific symptoms in the absence of objective clinical parameters

Serum cobalamin <150 ng/l
Further investigation & management as per algorithm 1

Serum cobalamin 150-200 ng/l

Serum cobalamin in normal range:
No further investigation

Repeat serum cobalamin after 1-2 months

Persistent reduced serum cobalamin (150-200ng/l)

Check IFAB levels. Consider 4 weeks low dose (50mcg OD) oral cobalamin whilst waiting for IFAB results. Pts should be told to report immediately if symptoms of neuropathy develop as this dose is inadequate for true pernicious anaemia. Repeat serum cobalamin after 3-4 months

IFAB positive: treat as Pernicious Anaemia

IFAB negative:

Repeat serum cobalamin >200ng/l: NO FURTHER INVESTIGATION. Consider long-term low dose cobalamin therapy as for food malabsorption etc., as clinically indicated.

Repeat serum cobalamin 150-200ng/l:
This is a very difficult area. Seek causes for possible vitamin B12 deficiency other than Pernicious Anaemia (see over). Does not require treatment but monitor serum cobalamin infrequently. Check TTG & if positive or diarrhoea/abdo pain, refer to gastroenterology.

Serum B12 reference range in non-pregnant adults: 200-960ng/l

Abbreviations:

IFAB: Anti-Intrinsic Factor Antibody
TTG: Tissue Transglutaminase (coeliac screen)

Maintenance treatment with neurological symptoms:
IM hydroxocobalamin 1000mcg every 2 months for life. No further testing of B12 levels is necessary.
Oral cyanocobalamin is NOT recommended

Initial Treatment
Neurological symptoms present:
IM hydroxocobalamin 1000mcg alternate days until no more improvement (review after 3/52).
No neurological symptoms present:
IM hydroxocobalamin 1000mcg 3 x/wk for 2 weeks.

Maintenance treatment if haematological cause & no neurological symptoms & underlying cause not dietary: IM hydroxocobalamin 1000mcg every 3 months for life. No further testing of B12 levels is necessary. Also prescribe 5mg od folic acid for 1/12 to prevent folate deficiency developing.
Oral cyanocobalamin is not recommended

Maintenance treatment if dietary cause:
1000mcg hydroxocobalamin (IM) twice per year. In vegans, this may need to be life-long. Note that oral cyanocobalamin may not be suitable for vegans & is expensive. Its role in the treatment of subclinical deficiency is under active research.