

Investigation, treatment and review of Vitamin B12 (cobalamin) deficiency

IMPORTANT CONSIDERATIONS:

- B12 testing in patients with fatigue in the absence of anaemia/macrocytosis is unlikely to be useful, unless they have documented risk factors (e.g. (veganism, achlorhydria, gastric surgery, inflammatory bowel disease, FH of pernicious anaemia, autoimmune disease).
- 50% of low B12 results do NOT indicate true deficiency, so requestors must consider pre-test probability of B12 deficiency before making a request, otherwise the false positive result rate will be very high.
- ALWAYS ask about diet. Veganism is increasing. Give dietary advice to patients if thought to be diet related. Note that not all oral cyanocobalamin products are suitable for vegans.
- Consider periodic vitamin B12 monitoring in diabetic patients taking metformin with risk factors for vit. B12 deficiency (e.g. vegan diet, PPI usage, inflammatory bowel disease). -Not exhaustive see refs and page 3)

Treatment algorithm for NEW patients: (NB: BSW acute trusts all use different reference ranges for B12 levels, see box below*).

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

Algorithm 2: Patient with non-specific symptoms in the absence of objective clinical parameters (NB. Please see points 1 and 2 in "important considerations" box above)

- Serum cobalamin low*: Very probable deficiency
- Serum cobalamin borderline*: probable deficiency
- Serum cobalamin lower end of normal*: possible cobalamin deficiency. (i.e. falsely normal cobalamin) *see lab-specific ranges below.

Low serum cobalamin
Management as per algorithm 1

Borderline serum cobalamin

Repeat serum cobalamin after 1-2 months†

Persistent borderline serum cobalamin

Serum cobalamin in normal range:
No further investigation

Check IFAB levels.

Start cobalamin as per "initial treatment" box below

Check IFAB levels.

Consider 4 weeks low dose (100mcg OD) oral cyanocobalamin (bought OTC) whilst waiting for results. Advise patient to seek urgent medical attention if symptoms of neuropathy develop as this dose is inadequate for true 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.

IFAB positive:

Lifelong treatment as pernicious anaemia

Serum cobalamin normal:

NO FURTHER INVESTIGATION.
Consider long-term OTC low dose oral cyanocobalamin therapy.

IFAB negative:

Repeat serum cobalamin after 3-4 months

Serum cobalamin borderline:

Low B12 of unknown significance.
Seek causes for possible deficiency other than Pernicious Anaemia (see p3). Does not require treatment but monitor serum cobalamin 6-12 monthly. Check TTG & if positive or diarrhoea/abdo pain, refer to gastroenterology.

Treatment:

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 wks.

Maintenance treatment if haematological disease & no neurological symptoms & underlying cause not dietary:

IM hydroxocobalamin 1000mcg every 2-3 months. No further testing of B12 levels is necessary. **If dietary cause:** Review use of injection once stores are replenished to switch to oral cyanocobalamin (OTC) if possible. **Dietary or non-dietary cause:** If pt fails on injections†, consider Orobalin®

*Serum B12 reference range in non-pregnant adults (ng/L):

	GWH	RUH	SFT
Normal	181-914	180-914	197-771
Borderline	145-180	100-180	100-196
Low	<145	≤100	<100

Review/deprescribing in patients already receiving hydroxocobalamin injections

Review criteria for discontinuation of IM hydroxocobalamin that may have been initiated inappropriately:

- Patient was **asymptomatic or no associated pathology** at initiation
- Only **1 borderline result** for serum cobalamin (see individual acute trust reference ranges page 1)
- **IFAB negative** (where previously tested)

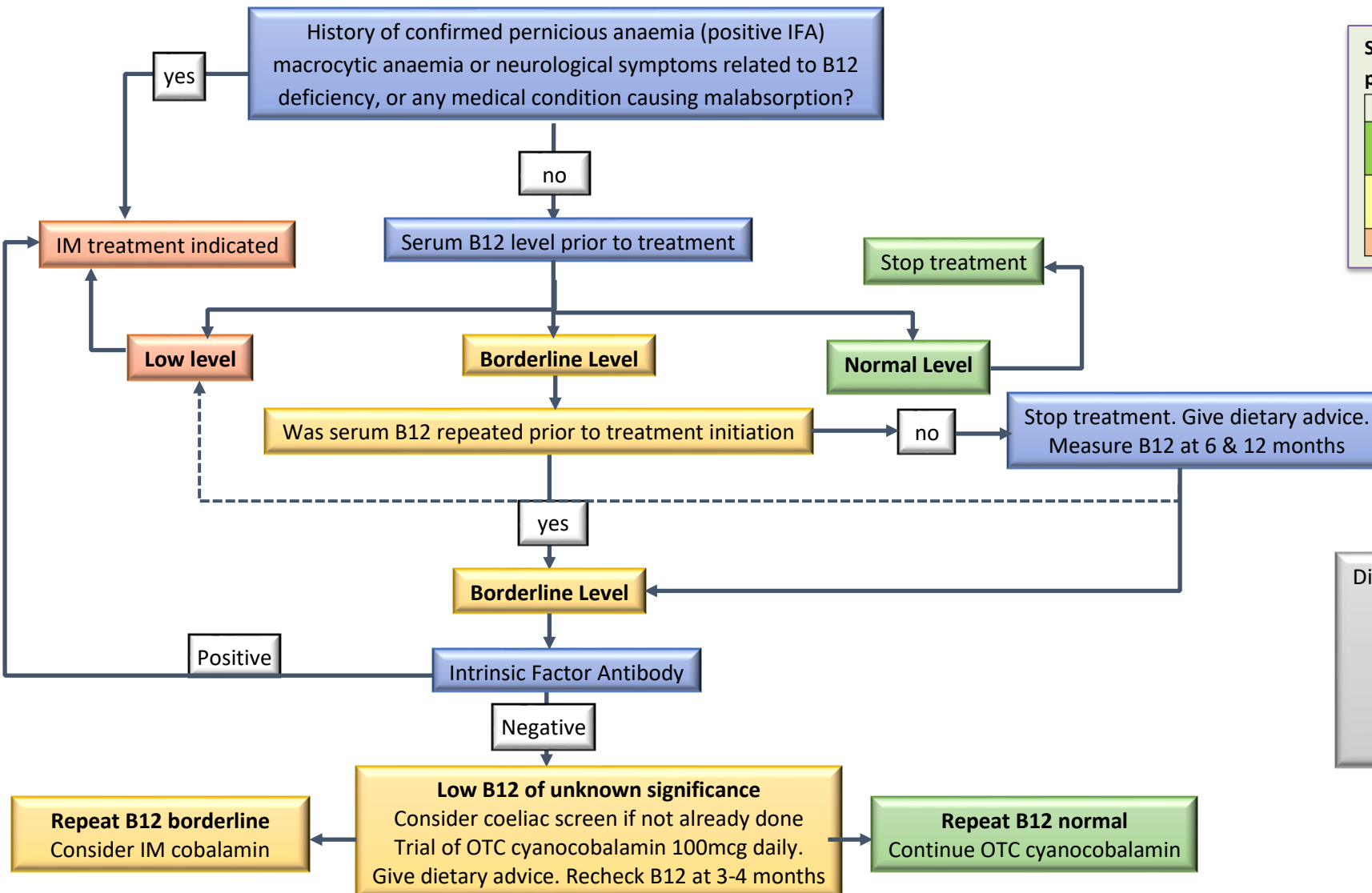
ALL 3 must apply

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Dietary sources of B12:

- Eggs, meat, fish, milk & other dairy products
- Fortified foods (e.g. some soy products, breakfast cereals & breads)



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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.
 - **Metformin:** Pragmatically, undertake B12 level monitoring for those on metformin with risk factors for deficiency or neuropathy during annual diabetes review.
- 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 (Apr 2022): <https://www.sps.nhs.uk/articles/vitamin-b12-deficiency-treatment-during-pregnancy/>

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>

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 Intrinsic Factor Antibodies (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 cyanocobalamin¹:

For any patient with *medically* diagnosed vitamin B12 deficiency (diet- or non-diet-related) or malabsorption of vitamin B12 where it is not possible to administer IM hydroxocobalamin, it is reasonable to prescribe oral cyanocobalamin (Orobalin[®]) on FP10. See [SPC](#) for full details.

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.

RUH Haematology helpline: 07789 928466
SFT: shc-tr.haemenquiries@nhs.net
GWH: gwh.haematologyadvice@nhs.net 01793 607425

Primary Care: Resources to support practices to review hydroxocobalamin prescribing can be found [here](#)

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>
- ***MHRA DSU June 2022:** Metformin and reduced vitamin B12 levels: new advice for monitoring patients at risk
- Oral vitamin B12 – what are the prescribing considerations and what formulations are available? Medicines Q&As UKMi SPS. May 2020.
[UKMI QA Oral-Vitamin-B12-preparations May-2020.pdf \(sps.nhs.uk\)](http://www.ukmi.org.uk/qa/oral-vitamin-b12-preparations-may-2020.pdf)