BNSSG Vitamin B12 deficiency guidelines

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1. Who should be considered for testing?

At least one common symptom or sign + at least one common risk factor

Signs and Symptoms

- **FBC abnormalities** (anaemia / macrocytosis – *although these are not always present in B12 deficiency*)
- **Cognitive difficulties** (difficulty concentrating / dementia symptoms/ brain fog)
- **Impaired eyesight** (blurred vision / optic atrophy / visual field loss)
- **Glossitis**
- **Neurological symptoms** (balance / gait problems / falls / pins and needles / peripheral neuropathy)
- **Unexplained fatigue**
- **Mental health** (anxiety, depression, psychosis)
- Symptoms or signs of anaemia that suggest iron treatment is not working properly during pregnancy or breastfeeding (measure Active B12 in pregnant individuals, see section 2)

Risk factors/causes

- **Low B12 diet** (vegan / restricted diet / malnutrition)
- **Malabsorption** (atrophic gastritis / coeliac disease [consider TTG testing if not already completed] / Crohn's Dx)
- **Previous GI surgery** (bariatric / gastrectomy / terminal ileal resection) – other GI surgery are not considered risk factors unless impairing B12 absorption
- **Previous radiotherapy** of the abdomen or pelvis
- **Medications** – see Appendix 2 for further information. Colchicine / H2 receptor agonists / metformin [See section 5 for management] / phenobarbital / pregabalin / primidone / PPIs / topiramate)
- **Nitrous oxide** (NO) abuse
- **Autoimmune disease** (thyroid disease / Sjogrens / T1DM)
- **Family history** of B12 deficiency or autoimmune conditions

2. Testing strategy

- Total Vitamin B12 is poorly performing, and measured concentrations do not always correlate with intracellular B12 levels
- **There is substantial variation between Total Vitamin B12 analytical methods, hence local reference ranges must be used for the local analytical method and NICE NG239 thresholds do not apply** (because of the local method performing much lower compared with other analytical methods)
- Combined oral contraception pill (COCP) can lower Total B12 levels **without** deficiency being clinically present (i.e. give a falsely low B12 result) due to a common carrier protein but deficiency may be concurrently present (suggest 6/52 washout from COCP if required).
- Active B12 is indicated only in pregnant individuals as first line (normal range on report)
- Be aware that people of black ethnicity may have a higher Total B12 level, so may have deficiency clinically despite a "normal Total B12 result" – discordance between B12 level and clinical state may be more likely so have a lower threshold for trial of treatment

Total B12 first line for majority	Active B12 first line in pregnant individuals (available to request from Summer 2025)	MMA (or tHCy) if 2nd line testing required or if NO abuse –> Section 4 (Total/active B12 may be normal)

3. Initial interpretation of Total B12

B12 normal (> 180 nanograms/L)	**Deficiency unlikely**	Reassure and look for alternative causes for symptoms If ongoing symptoms 3-6 months later consider a repeat test
B12 indeterminate (Between 145 and 180 nanograms/L). GP population differs from 2ndry care cohort; a larger proportion of indeterminate results may be normal or due to dietary restrictions; they can be given OTC B12 and followed up in 6 months.	**Observe pathway** **If non-specific symptoms and/or low clinical suspicion**	Suggest dietary improvements and signpost to NHS website:NHS webpage on B vitamins The patient may consider OTC B12. Advise return if develop symptoms or signs, consider repeat B12 in 6 months +/- 2nd line test. If treatment then needed -> use "non-specific symptoms" pathway in section 5..
	Treatment pathway **If objective symptoms and/or strong clinical suspicion**	Ensure Intrinsic Factor Antibodies measured prior to treatment if not tested previously and no history of GI surgery. If concern regarding diagnosis -> consider discussion with duty biochemist about MMA testing. Proceed to Step 5 for treatment guidelines.
B12 low (< 145 nanograms/L)	**Deficiency likely**	Test Intrinsic factor antibodies (+/- Coeliac screen if coeliac possible) if not tested previously and no history of GI surgery. Go to Step 5 for treatment..

4. Further investigations

Coeliac screen	• Coeliac screen could be an underlying cause of malabsorption causing low B12 • Consider TTG as part of further biochemical testing only if clinically indicated
Intrinsic factor antibodies (IFA)	• Intrinsic factor antibodies are required on all patients when B12 <145ng/L OR persistent indeterminate B12 results after 6 months OR after a high Methylmalonic Acid (MMA) result. • Isolated low Ferritin is not a reason to test intrinsic factor antibodies • If autoimmune gastritis (Pernicious anaemia) is still suspected despite a negative intrinsic factor antibody consider anti-gastric parietal cell antibodies, gastrin (specialist collection requirements). **Do not test intrinsic factor antibodies within 2 weeks of IM injection as this will give a false positive result.**
MMA or tHCy Testing 2nd line? MMA is preferred for primary care testing.	• Both Methylmalonic Acid (MMA) and Total Homocysteine (tHCy) are possible 2nd line tests for evaluating intracellular concentrations of B12 • tHCy elevation can be seen earlier than a rise in MMA in the clinical course of B12 deficiency, when evaluating intracellular levels, but it is impractical to sample from primary care without secondary care phlebotomy, as samples **must** be sent on ice to the laboratory to be separated urgently • MMA has easier sample handling (serum/plasma sample that can be added on) and thus is the preferred 2nd line test (and recommended by NICE guidance) • MMA has **not been formally commissioned** so only available if there is discordance between biochemistry (Total/active B12) and clinical state and/or where a trial of supplementation is not adequate. • MMA requests should ideally be discussed with the Duty Biochemist in advance and may be rejected if not appropriate • If MMA confirms deficiency then IFA should be tested if not already done so

5. Treatment strategies (see Appendix 3 for costs)

Do not delay vitamin B12 replacement for people with megaloblastic anaemia or neurological symptoms, especially symptoms related to sub-acute combined degeneration of the spinal cord (secondary to NO abuse).
If anaemia or low folate present → use Folic Acid 5mg oral once daily alongside B12 for 4 weeks to prevent folate deficiency due to B12 replacement.

Pernicious Anaemia (PA) w/o neurological symptoms **OR** malabsorption (due to GI surgery or other cause) **OR** pregnancy **OR** medication induced (if IM replacement indicated- Appendix 2)	• 1mg Hydroxycobalamin IM 3 times per week for 2 weeks then once every 2-3 months. Adjust frequency according to effect. • In pregnancy, 1mg PO dose can be alternative (click for link). • If malabsorption or pregnancy -> stop B12 if/when resolved • In coeliac -> consider de-escalation to oral, or stopping B12, if/when symptoms improve • If PA -> lifelong B12
PA with neurological symptoms **OR** NO abuse	1mg Hydroxycobalamin alternate days IM for 2 weeks then 1mg every 1-3 months. If PA -> lifelong B12.
Tobacco Amblyopia or Leber's optic atrophy	1mg Hydroxycobalamin daily IM for 2 weeks then 1mg every 1-3 months. Lifelong replacement.

IFA negative megaloblastic ± anaemia with Total B12 <180ng/L **OR** dietary cause **OR** medication induced (if PO indicated – Appendix 2)	Cyanocobalamin 50-100mcg (see Appendix 3 for costs) and recheck FBC/symptoms in 2 months. Consider stopping B12 if/when cause resolved.	If no response, consider 1mg Hydroxycobalamin IM 3 times per week for 2 weeks then once every 2-3 months. Stop B12 if/when cause resolved.
Non-specific symptoms not meeting any other criteria above. For further advice on treatment duration see section 6.	1st line: Cyanocobalamin 50-100mcg daily and check if symptomatic response clinically in 2 months – see section 6. 2nd line: Cyanocobalamin 1mg daily could be trialled if no response on initial dose. **This should not be considered first line dosing. Only consider first line dosing if wishing oral preparation in pregnancy.** If symptoms still not improving on max oral 1mg dose, consider switch to IM replacement for trial period. Review in 3-6 months and consider stopping B12 if symptoms resolve.	

6. Follow-up of treatment response

Review symptoms (+FBC if anaemia present) 3 months after starting treatment (1 month if pregnant or breastfeeding).

Do not repeat Total B12 testing once replacement started.

Symptoms improved or resolved

If cause irreversible or not known - continue replacement –> this may be lifelong but consider regular review period if necessary (e.g. yearly) so not continued long term without review.

Consider stopping treatment if:
- Symptoms resolved so they are no longer affecting daily activities
- The cause, or suspected cause has been resolved (e.g. malabsorption or medication)

Symptoms not improved

New or worse symptoms

Consider other causes of symptoms (See Step 1)

Consider either increase oral dose to maximum (such as 1mg PO once daily), switch to IM (see IFA negative indeterminate or low B12 approach in Step 5), or increase frequency of IM (such as Pernicious anaemia w/o neuro symptoms approach in step 5). Consider MMA to confirm deficiency (see Step 4).

References:

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3. Vitamin B12 defificiency – information for clinicians – Royal United Hospitals Bath NHS Foundation trust – URL: https://www.ruh.nhs.uk/pathology/documents/clinical_guidelines/PATH-029_B12.pdf. Accessed: May 2025
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6. British Society of Haematology, "Diagnosis of B12 and Folate deficiency", 2024 URL: https://b-s-h.org.uk/guidelines/guidelines/diagnosis-of-b12-and-folate-deficiency. Accessed May 2025

Appendix 1: Elevated B12 levels

This is often a non-pathological finding and rarely due to a haematological condition. The most common cause of high vitamin B12 in the absence of B12 replacement therapy is liver disease. Vitamin B12 may be elevated in haematological malignancy including myeloproliferative disorders and these disorders are excluded by a normal FBC.

Assessment in Primary Care

Check that the patient has not been taking supplements that include vitamin B12.
Assess general health and for risk factors for liver disease.

Investigations in Primary care:

These will be determined by the clinical history examination and blood results. Unless a haematological malignancy is suspected from the FBC report, discussion with or referral to Haematology is not required. Assessment for liver disease may be appropriate.

Appendix 2: Medication induced B12 deficiency mechanism of action and route of replacement administration. Section author: Safeeya Mohamed (Bristol inner city PCN pharmacist)

In cases where medication induced B12 deficiency is seen – review if the medication can be stopped but continue supplementation while using the drug.
Consider stopping B12 replacement once medication stopped +/- any associated symptoms resolved.

Drug	Administration route of B12 replacement if required	Mechanism of B12 deficiency
Anti-epileptic drugs: Phenobarbital Primidone Pregabalin Topiramate	Oral	• Mechanism unknown • Oral B12 and folate supplementation normalise B12 and homocysteine plasma levels (Linnebank et al, 2011)
Colchicine	Oral or IM	• Inhibits B12 absorption by reducing intrinsic factor receptor levels in the ileum. • However, few studies have reported significant colchicine-induced B12 deficiency in humans (Busti, 2015; Jung et al, 2022).
H2 Receptor Antagonists (H_2RA) & Proton Pump inhibitors (PPI)	Oral	• Increase the gastric pH impairing activation of pepsinogen to pepsin which releases B12 from ingested proteins. • The absorption of unbound B12 is not inhibited, so oral B12 supplementation can be used while taking gastric acid-suppressing medication. • Taking H_2RAs or PPIs for more than 2 years significantly increases risk of B12 deficiency (Miller, 2018).
Metformin	Oral or IM	• Decreases calcium-dependent uptake of B12/intrinsic factor complex within the terminal ileum of the small intestine (Busti, 2015; Pratama et al, 2022; Sayedali et al, 2023). • It is believed it takes at least 5 years for metformin to deplete B12 reserves (Sayedali et al, 2023). • A randomised controlled trial showed Oral Methylcobalamin 1000mcg (1mg)/day for 1 year significantly increases B12 levels and improves neuropsychological parameters (Jung et al, 2022, Sayedali et al, 2023)

Appendix 3: BNSSG Formulary tariff costs for B12 replacement preparations

Correct as of May 2025

Drug	Drug Tariff price (as per May 2025)
Cyanocobalamin 50microgram tablets	£2.60/50 tablets
Cyanocobalamin 1mg tablets	£9.99/30 tablets
Hydroxocobalamin 1mg/1ml solution for injection ampoules	£11.16/5 ampoules