

BOX 1: Some Reasons to Measure B12:

- ↑ MCV*, anaemia, cytopenia
 - Clinical symptoms e.g. peripheral neuropathy, ataxia, paraesthesia, impaired gait, glossitis, blurred vision, scotoma, 'brain fog', unexplained fatigue
 - Risk factors for B12 deficiency (BOX 2)
 - Folate deficiency
- *↑ MCV is not specific for B12 deficiency. Other causes include alcohol excess, anti-neoplastic drugs & myelodysplasia.
*↑ MCV may be absent in B12 deficiency.

BOX 2: Main Causes of B12 deficiency

- Autoimmune gastritis (commonest cause – aka pernicious anaemia)
- Dietary; inadequate intake (e.g. vegan).
- Medicines; e.g. [metformin](#), H2-receptor antagonists & PPIs, colchicine, anticonvulsants (pregabalin, primidone, phenobarbital, topiramate), neomycin.
- Malabsorption: Gastrectomy; Ileal resection; Coeliac; Crohn's; Bariatric surgery.
- Recreational **nitrous oxide use**; N₂O oxidises B12 rather than destroying it, so vitamin B12 levels may be normal, but functionally inactive. Patients present with neurological abnormalities/subacute combined degeneration of the cord[§] requiring **emergency** assessment, treatment & investigations for B12 deficiency.

It is also important to note that:

- Patients on the **oral contraceptive pill/HRT** may show decreased B12 levels due to decreased cobalamin carrier protein, rather than a deficiency state.
- B12 levels may be falsely low in **pregnancy** because of the increased plasma volume of pregnancy rather than actual deficiency. This makes it very difficult to diagnose vitamin B12 deficiency in pregnancy.

BOX 3: Management in Primary Care

Do not delay B12 replacement whilst waiting for test results in suspected megaloblastic anaemia and neurological symptoms, especially those related to subacute combined degeneration of the cord[§] (including patients abusing nitrous oxide) (See BOX 4).

B12 Replacement:

For people with neurological involvement: Initially IM* hydroxocobalamin 1mg once daily on alternate days until no further improvement then *maintenance* IM* hydroxocobalamin 1mg every 2 months

For people without neurological involvement:

- a) **Autoimmune gastritis or Malabsorption-induced:** Initially IM* hydroxocobalamin 1 mg 3 times a week for 2 weeks, then *maintenance* IM* hydroxocobalamin 1mg every 2–3 months
- b) **Diet:** *First line Dietary advice* (as below[#]). *Second line.* Advise to **purchase over the counter (OTC)** oral B12 50–150 micrograms once daily (dose may be increased where clinically appropriate) or IM* hydroxocobalamin 1mg twice a year (if concerns about adherence or if person's clinical condition may deteriorate). In vegans, treatment may need to be lifelong. In other dietary causes treatment can be stopped once B12 is corrected and diet has improved.
- c) **Medicine-induced:** **Either** IM* hydroxocobalamin 1 mg 3 times a week for 2 weeks, then *maintenance* IM* hydroxocobalamin 1mg every 2–3 months **or** daily oral B12, (based on clinical judgement and the person's preference, while they are taking the medicine causing the deficiency). Review the use of the medicine to see if it is still needed or can be changed.
- d) **Deficiency of unknown cause:** Initially IM* hydroxocobalamin 1 mg 3 times a week for 2 weeks, then *maintenance* either IM* hydroxocobalamin 1mg every 2–3 months **or** oral B12 (*preferred*) 500-1000mcg daily, (based on clinical judgement and the person's preference).

In all cases, a shared decision-making approach should take place between the clinician and patient. If B12 deficiency is dietary related, advise patient to purchase oral B12 OTC. (containing at least 1 of the following types of vitamin B12; cyanocobalamin, methylcobalamin, adenosylcobalamin). For other indications, or where there are compliance concerns, if oral B12 is to be prescribed, prescribe the most cost-effective formulation at the time of prescribing.

Note: Patients presenting with severe anaemia may develop a transient hypokalaemia following treatment. Do not give oral B12 replacement if IFA positive or high suspicion of autoimmune gastritis (pernicious anaemia).

* Further testing of B12 is not required in those on regular IM replacement.

Dietary advice: e.g. meat, salmon and cod, dairy, eggs, fortified foods (yeast products, breakfast cereals, soy products). Further information can be found via the [NHS website](#) or the [vegetarian society website](#).

Serum B12 in Adult Non-Pregnant Patient with Signs, Symptoms or Risk Factor (see BOX 1 & 2)

B12 Indeterminate:
197-350 ng/L

NB People already taking OTC vitamin B12 may have an increased B12 result without fully treating the deficiency; consider when interpreting results.

STH reference range in non-pregnant adults: 197-771 ng/L
NB. People of Black ethnicity may have a higher reference range for vitamin B12 than people of White or Asian ethnicity.

B12 Deficient:
<197 ng/L
Check folate in case of folate deficiency

- Consider vitamin B12 replacement for people who have an initial test result that is indeterminate and meet any of the following criteria:
 - i. they have signs or symptoms that may deteriorate rapidly and have a major effect on quality of life (e.g. megaloblastic anaemia, cytopenia or neurological symptoms)
 - ii. they have a condition or suspected condition that is an **irreversible cause** of vitamin B12 deficiency (e.g. [autoimmune gastritis](#))
 - iii. they have had surgery that can cause vitamin B12 deficiency (e.g. gastrectomy, terminal ileal resection or some types of bariatric surgery).
- Advise people with no symptoms or signs of vitamin B12 deficiency and an indeterminate B12 result to seek medical help if they develop symptoms or signs of deficiency.

The duty biochemist, haematologist and immunologist can be contacted via switchboard (243 4343)

- Replace with B12 (see BOX 3).

- Check TFTs.
- If also folate deficient give B12 replacement first.
- For people with confirmed vitamin B12 deficiency, consider an anti-intrinsic factor antibody (IFA) test if autoimmune gastritis is suspected and they have **not** previously had:
 - A positive anti-IFA test at any time, or
 - An operation that could affect vitamin B12 absorption (such as total gastrectomy or complete terminal ileal resection).
- Also consider checking for serum anti-IFA if strong clinical features of B12 deficiency, such as megaloblastic anaemia or subacute combined degeneration of the cord, despite a normal B12. NB About **50%** with autoimmune gastritis (pernicious anaemia) will have IFA. If IFA is present, autoimmune gastritis is very likely, but its absence does not rule out a diagnosis.
- Offer serological testing for coeliac disease where the cause of vitamin B12 deficiency is still unknown

[§]**Subacute combined degeneration of the spinal cord commonly presents with sensory deficits, paraesthesia, weakness, ataxia, and gait disturbances**

BOX 4: Suggested Referral Pathways:

- Refer to SDEC if suspected nitrous oxide toxicity (see BOX 2).
- Neurology: D/w neurology on-call if suspected subacute combined degeneration of the cord[§] or neurological symptoms, or if the diagnosis is unclear.
- Obstetrics if pregnant (see BOX 2).
- Haematology if the cause is uncertain following investigations, or suspected cause is haematological malignancy (urgently refer) or other blood disorder.
- Gastroenterology if malabsorption is suspected or if there is a suspicion of gastric cancer

References: 1. [Anaemia - B12 and folate deficiency | Health topics A to Z | CKS | NICE](#) (last accessed June 2025) 2. [Overview | Vitamin B12 deficiency in over 16s: diagnosis and management | Guidance | NICE](#) (March 2024) 3. [Wolffenbuttel BHR et al. Vitamin B12. BMJ 2023; 383.](#) 4. [Devalia V et al. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. Br J Haematol. 2014; 166: 496-513](#) 5. [BNF \(British National Formulary\) | NICE](#)

Author: Dr Hannah Delaney, Consultant, Clinical Chemistry, Sheffield Teaching Hospitals NHS Foundation Trust.

Authors of BOX 3: Management: Kirsty Burdett, Heidi Taylor, Shameila Asfar-Baig. Medicines Optimisation Team, Sheffield Place, SYICB LMGPR0023 Version 4; Feb 2026. Review: Feb 2031.

