

# B12 deficiency diagnosis and management: A review of updated guidelines

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# NICE B12 DEFICIENCY GUIDELINES PUBLISHED MARCH 2024

[HTTPS://WWW.NICE.ORG.UK/GUIDANCE/NG239](https://www.nice.org.uk/guidance/ng239)

## **Patient messages to healthcare professionals...**

1. Listen to patients when they say treatment is too infrequent
2. Necessity for General Practitioners to recognize and understand symptoms
3. Lack of awareness of the emotional and day-to-day effects of the condition
4. Include tests for B12 levels in standard blood test
5. Listen to patient (don't discount because symptoms are wide ranging, vague and invisible)
6. Understand co-morbidity of B12 deficiency and other conditions (IBS, depression, vitamin deficiencies)
7. Please take condition seriously
8. The effect of social media on patient experience and behaviour
9. Gain greater knowledge of co-factors associated with B12 deficiency
10. Don't discount the patient experience or their own research
11. Recognize that health-care professionals can't know everything about every condition
12. Educate all health-care professionals about B12 deficiency and blood tests
13. Awareness that the UK blood test range is very low (compared to other countries)

# KEY RECOMMENDATIONS REGARDING INFORMATION AND SUPPORT

[HTTPS://WWW.NICE.ORG.UK/GUIDANCE/NG239](https://www.nice.org.uk/guidance/ng239)

Explain to people with **suspected vitamin B12 deficiency** that:

- The symptoms and signs of vitamin B12 deficiency may also be associated with many other conditions
- ***A single blood test can be enough to support a diagnosis of vitamin B12 deficiency, but some people may need further tests to diagnose the condition.***

Explain to people with **confirmed Vitamin B12 deficiency** that:

- Vitamin B12 deficiency affects each person differently
- It can be caused by either, or both, a lack of vitamin B12 in the diet or problems with the way the body processes the vitamin that are linked to certain medications, operations, conditions or the recreational use of nitrous oxide
- Symptoms can affect daily activities, family and social life, work and education

# KEY RECOMMENDATIONS REGARDING INFORMATION AND SUPPORT

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- Treatment with vitamin B12 replacement is effective in most people
- ***For some, the dose, frequency and way vitamin B12 replacement is given may need to be adjusted or changed for it to work properly***
- It is important to continue with treatment as advised so that symptoms do not return or get worse
- People with some causes of vitamin B12 deficiency will need (and should receive) lifelong vitamin B12 replacement, such as deficiency caused by autoimmune gastritis

# RECOGNISING VITAMIN B12 DEFICIENCY

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Be aware that symptoms and signs of vitamin B12 deficiency:

- Can vary from person to person **and**
- Are often not exclusive to vitamin B12 deficiency.

Take into account that vitamin B12 deficiency is highly likely in people after total gastrectomy or complete terminal ileal resection, if they are not receiving either oral or intramuscular vitamin B12 replacement.

***Do not rule out a diagnosis of vitamin B12 deficiency based solely on the absence of either anaemia or macrocytosis.***

Be aware that vitamin B12 deficiency can be associated with mental health problems, including symptoms of depression, anxiety or psychosis.

# WHEN TO TEST

[HTTPS://WWW.NICE.ORG.UK/GUIDANCE/NG239](https://www.nice.org.uk/guidance/ng239)

Offer an initial diagnostic test for vitamin B12 deficiency to people who have:

- At least 1 common symptom or sign (see [box 1](#)) **and**
- At least 1 common risk factor for the condition (see [box 2](#)).

Use clinical judgement when deciding whether to test people who have at least 1 common symptom or sign (see box 1) but no common risk factors (see box 2)

# WHEN TO TEST

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- *Note: Evidence base was low quality or very low quality but results of studies reviewed were in line with expectations and clinical experience of the committee. In the absence of evidence, the committee used their own expertise and experience to recommend that people should be tested for vitamin b12 deficiency if they present with at least 1 risk factor and at least 1 symptom or sign. **Risk factors, symptoms and signs are not always a clear indication of a vitamin B12 deficiency, but the committee agreed that the presence of at least 1 risk factor and 1 symptom or sign increases its likelihood.***
- *The committee noted that **some people with symptoms and signs but no risk factors may still have a deficiency.** Some may also be unaware of any risk factors they have. The committee agreed that testing could be an option for people who do not have any of the common risk factors associated with a deficiency. However, they also agreed it was important to use clinical judgement in deciding when to test because the symptoms and signs of vitamin B12 deficiency are shared by many other conditions.*
- *In the absence of evidence, the committee used their experience and expertise to agree a list of symptoms and signs commonly associated with vitamin B12 deficiency. This will help prompt suspicion of the condition and in turn help ensure it is caught early, preventing any further deterioration.*

# BOX 1: COMMON SYMPTOMS AND SIGNS OF VITAMIN B12 DEFICIENCY

[HTTPS://WWW.NICE.ORG.UK/GUIDANCE/NG239](https://www.nice.org.uk/guidance/ng239)

Abnormal findings on a blood count such as anaemia or macrocytosis

Cognitive difficulties such as difficulty concentrating or short-term memory loss (sometimes described as 'brain fog'), which can also be symptoms of delirium or dementia

Eyesight problems related to optic nerve dysfunction:

- Blurred vision
- Optic atrophy
- Visual field loss (scotoma)

Glossitis

Neurological or mobility problems related to peripheral neuropathy, or to central nervous system disease including myelopathy (spinal cord disease):

- Balance issues and falls caused by impaired proprioception (the ability to sense movement, action and location) and linked to sensory ataxia (which may have been caused by spinal cord damage)
- Impaired gait
- Pins and needles or numbness (paraesthesia)

Symptoms or signs of anaemia that suggest iron treatment is not working properly during pregnancy or breastfeeding

Unexplained fatigue.



# BOX 2: COMMON RISK FACTORS FOR VITAMIN B12 DEFICIENCY

[HTTPS://WWW.NICE.ORG.UK/GUIDANCE/NG239](https://www.nice.org.uk/guidance/ng239)

**Diet low in vitamin B12** (without the regular use of over-the-counter preparations), for example, in people who:

- Follow a diet that excludes, or is low in, animal-source foods (such as a vegan diet, or diets excluding meat for religious beliefs)
- Do not consume food or drinks fortified with vitamin B12
- Have an allergy to some foods such as eggs, milk or fish
- Find it difficult to buy or prepare food (for example, people who have dementia or frailty, or those with mental health conditions)
- Find it difficult to obtain or afford foods rich in vitamin B12 (for example, people on low income)

- Have a restricted diet (for example, because of an eating disorder)

## **Family history of vitamin B12 deficiency or an autoimmune condition**

### **Health conditions:**

- Atrophic gastritis affecting the gastric body
- Coeliac disease or another autoimmune condition (such as thyroid disease, Sjögren's syndrome or type 1 diabetes)
- *Previous abdominal or pelvic radiotherapy*

### **Previous gastrointestinal surgery:**

- Many bariatric operations (for example, roux-en-y gastric bypass or sleeve gastrectomy)
- Gastrectomy or terminal ileal resection

### **Recreational nitrous oxide use**

# BOX 2: COMMON RISK FACTORS FOR VITAMIN B12 DEFICIENCY

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## Medicines:

- Colchicine
- H<sub>2</sub>-receptor antagonists
- Metformin (see the [MHRA safety advice on metformin and reduced vitamin B12](#))
- Phenobarbital
- Pregabalin
- Primidone
- Proton pump inhibitors
- Topiramate

## Note:

*There is a lack of evidence on how recreational nitrous oxide use affects vitamin B12 deficiency because it is difficult to undertake prospective studies in this area. **However, nitrous oxide is known to inactivate vitamin B12 in the body. The committee also acknowledged that recreational use of nitrous oxide is a significant public health issue.** In light of this, and based on their experience and expertise, they highlighted recreational nitrous oxide use as a potential risk factor but agreed that more research is needed into the effects of the substance, particularly if it is used regularly or in large amounts.*

*The committee discussed whether to include age in the list of risk factors. **They acknowledged that the ageing process causes physiological changes in the gastrointestinal system that can affect dietary intake of vitamin B12 and can potentially cause malabsorption.** Older people are also at higher risk of developing health problems that can impact on their diet and eating habits, such as cognitive impairment or dementia. Using their experience and expertise, they highlighted some important symptoms, signs and risk factors that can affect people aged 65 and over. However, they agreed that age was not a risk factor in itself and would not warrant a test for deficiency without the presence of other risk factors, or signs or symptoms.*

# FREQUENTLY REPORTED SIGNS AND SYMPTOMS B12 DEFICIENCY CITED IN BMJ REVIEW

[HTTPS://WWW.BMJ.COM/CONTENT/383/BMJ-2022-071725](https://www.bmj.com/content/383/bmj-2022-071725)

(VITAMIN B12 (PRACTICE THERAPEUTICS PUBLISHED 20 NOVEMBER 2023))

- **Brain function:** “brain fog,” memory problems, cognitive impairment, ***insomnia, headaches (especially migraine), behavioural changes, learning problems, nominal aphasia***
- **Mood:** mood swings, irritability, depression, anxiety, hallucinations, delusions, psychosis
- **Sensory:** peripheral paraesthesia (“pins and needles”), numbness, neuropathic pains, poor balance, reduced vibration sense or proprioception (joint position sense), ***tinnitus***, ataxia, ***taste impairment***, sometimes myelopathy
- **Constitutional:** fatigue, anaemia (either macrocytic, or normocytic when also iron deficient or associated with thalassaemia minor), ***other cytopenia, abdominal complaints, malabsorption, failure to thrive, weight loss, diarrhoea, hyperpigmentation***, glossitis, ***(aphthous) stomatitis, infertility, urinary tract infections***
- **Motor:** muscle weakness, altered reflexes (increased in degeneration of the spinal cord, reduced when peripheral neuropathy dominates), spasticity, ***seizures, cardiomyopathy***
- **Autonomic:** ***urinary and/or faecal incontinence, postural hypotension or dizziness, erectile dysfunction***

## Functions of vitamin B12

Energy production

Blood

Cell division

Brain

Immune system

## Symptoms and signs of vitamin B12 deficiency

85%

### Cognition

Memory problems, cognitive impairment, nominal aphasia, learning problems, headaches and migraines

### Mental Health

Mood swings, irritability, insomnia, depression, anxiety, hallucinations, delusions

### Neurological

Parasthesia, numbness, poor balance, tinnitus, ataxia, myelopathy, spasticity, autonomic dysfunction

15%

### Blood

Pancytopenia, macrocytosis, hypersegmented neutrophils

### Bone marrow

Hyperplasia, megaloblastic features

### Tongue\*

Glossitis, taste impairment, (aphthous) stomatitis

### Other\*

Abdominal complaints, poor appetite, weight loss, infertility, hyperpigmentation

\*Prevalence variable

## Prevention

When dietary B12 intake is inadequate, eg. plant-based diets, or taking medications that interfere with B12 absorption

Oral supplementation w. cyanocobalamin once daily 20-50 mcg

## Treatment

### When symptoms and deficiency

Start w. hydroxocobalamin\* i.m. injections 1000 mcg on alternate days (UK)

### When neurological symptoms

Continue B12 injections i.m., every other day, until symptoms have subsided/ do not improve further, then slowly reduce injection frequency

### When anaemia only

Gradually reduce injection frequency after 2-5 weeks; maintenance: 1000 mcg i.m. every 4-8 weeks

\*In USA mainly cyanocobalamin  
\*In NL twice-weekly

## Follow-up

### Monitoring

Be alert for other deficiencies (B2, folate, iron, D3)

### Individualized

Long-term maintenance may vary from 2x/week to 1x/4 weeks 1000 mcg B12 i.m.

### Teach self-administration†

Relatively easy and aids in remaining symptom-free

Note: skin hyperpigmentation, most commonly affecting dorsal aspects of hands and feet with knuckle hyperpigmentation being most prominent, can occur alone in absence of other signs of b12 deficiency. Elbows and knees can also be affected.

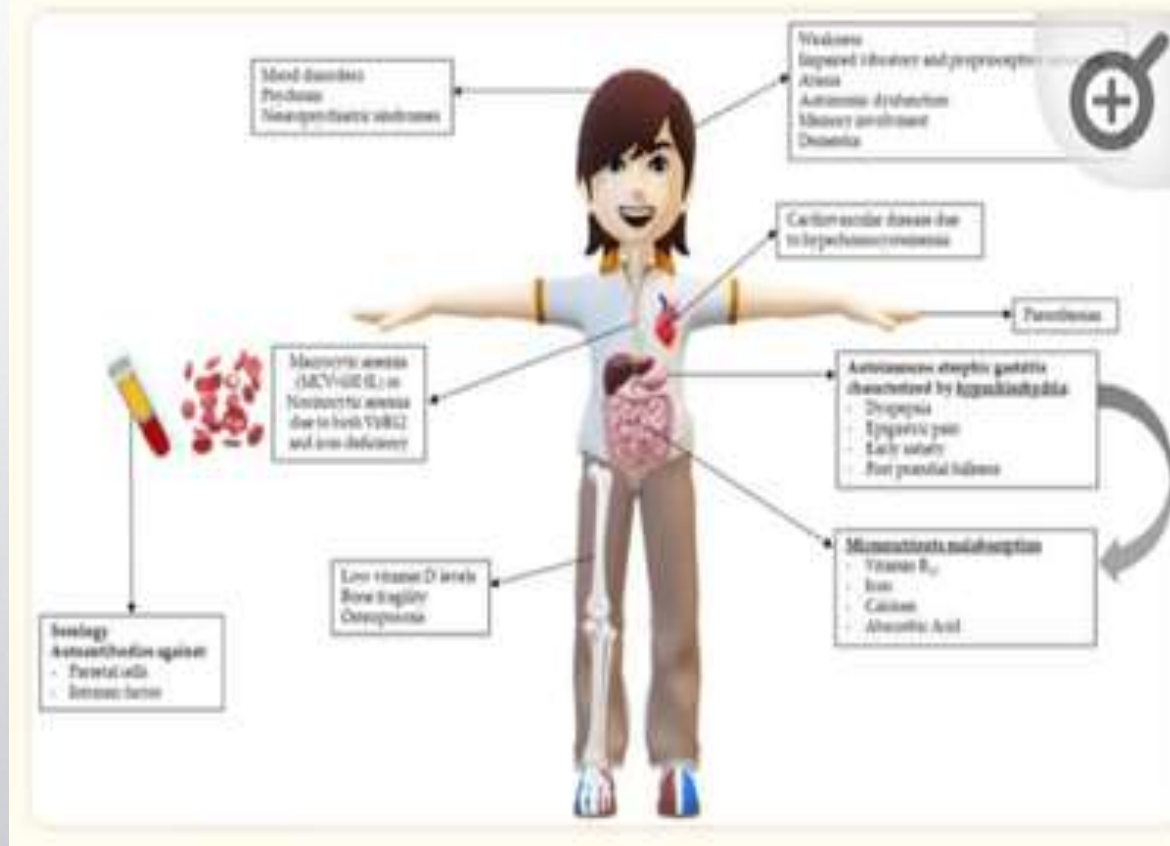
It is more common in darker skinned individuals. See link for an interesting case report.

<https://www.cureus.com/articles/112515-hyperpigmentation-as-a-primary-symptom-of-vitamin-b12-deficiency-a-case-report#!/>

[HTTPS://WWW.BMJ.COM/CONTENT/383/BMJ-2022-071725](https://www.bmj.com/content/383/bmj-2022-071725)

**Pernicious Anemia: The Hematological Presentation of a Multifaceted Disorder Caused by Cobalamin Deficiency.** Published April 2022. – <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9030741/>  
*An interesting read – highlights the fact that achlorhydia /hypochlorhydia due to atrophic gastritis caused by PA can reduce iron, vitamin d, calcium and vitamin c absorption.*

Main clinical consequences in patients with Pernicious Anaemia related to hypochlorhydia and vitamin B12 deficiency – Image is from the above link / article.



# DIAGNOSING B12 DEFICIENCY

[HTTPS://WWW.NICE.ORG.UK/GUIDANCE/NG239](https://www.nice.org.uk/guidance/ng239)

## Initial tests

Use either total B12 (serum cobalamin) or active B12 (serum holotranscobalamin) as the initial test for suspected vitamin B12 deficiency unless:

- The test needs to be done during pregnancy, or
- Recreational nitrous oxide use is the suspected cause of deficiency.

Use active B12 as the initial test for suspected vitamin B12 deficiency during pregnancy.

If the person has suspected vitamin B12 deficiency caused by recreational use of nitrous oxide:

- Use plasma homocysteine or serum methylmalonic acid (MMA) as the initial test and
- If using plasma homocysteine, refer the person to phlebotomy services in secondary care for this test.

# DIAGNOSING B12 DEFICIENCY

[HTTPS://WWW.NICE.ORG.UK/GUIDANCE/NG239](https://www.nice.org.uk/guidance/ng239)

Take blood samples for diagnostic tests before starting vitamin B12 replacement.

When offering an initial diagnostic test, ask the person if they are already using an over-the-counter preparation that contains vitamin B12 (including vitamin B12 tablets, injections or transdermal patches), and what type and dosage they are using. *Use caution when interpreting the total or active B12 test results of people who are already using an over-the-counter preparation containing vitamin B12 because this may increase total or active B12 concentrations without fully treating a deficiency.*

*Do not delay vitamin B12 replacement while waiting for the test results of people with **suspected megaloblastic anaemia and neurological symptoms, especially symptoms related to sub-acute combined degeneration of the spinal cord.***

Consider starting vitamin B12 replacement while waiting for the test results of people with suspected vitamin B12 deficiency that is a side effect of taking medicine.

# DIAGNOSING B12 DEFICIENCY

[HTTPS://WWW.NICE.ORG.UK/GUIDANCE/NG239](https://www.nice.org.uk/guidance/ng239)

## Note:

*The committee were aware that some test results need to be interpreted with caution but that some healthcare professionals may be unaware of this.*

*These include the total or active B12 test results of people who are already taking over-the-counter preparations containing vitamin B12, because **these can raise concentrations of the vitamin in the body and therefore mask a deficiency that has not been properly addressed.***

*Total B12 test results may also be affected by hormonal changes in the body caused by the combined oral contraceptive pill. **Taking the combined oral contraceptive pill can lower total B12 concentrations without causing a deficiency** (however, low total B12 concentrations may still mean the person has a deficiency).*



# DIAGNOSING B12 DEFICIENCY

[HTTPS://WWW.NICE.ORG.UK/GUIDANCE/NG239](https://www.nice.org.uk/guidance/ng239)

## DIAGNOSTIC TEST ACCURACY – VERY LOW QUALITY OF EVIDENCE FROM STUDIES

- *Evidence was identified for total B12 (cobalamin) as a first line test, active B12 (holotranscobalamin) as a first line test and second line test, methylmalonic acid (MMA) as a first line and second line test and homocysteine as a first line and second line test, for combinations of tests as first line tests and for active B12 and MMA as staged tests. No evidence was identified for women and people in the third trimester of pregnancy, afro-caribbean ethnicity, or males/females (homocysteine test).*
- *Several different reference ranges and cut-offs for index test positivity were reported in the studies. Out of ten studies included, no two studies used the same reference standard for defining deficiency. Reference standards included MMA/haematological response to treatment, total B12 concentration below the reference range, MMA concentration below the reference range, combinations of deficiency marker values and clinical abnormalities suggestive of deficiency. Some studies used MMA concentration as an index test, whereas others used it as the reference standard, making it difficult to triangulate the results across the studies.*

# DIAGNOSING B12 DEFICIENCY

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## DIAGNOSTIC TEST ACCURACY – VERY LOW QUALITY OF EVIDENCE FROM STUDIES

- *Evidence was of very low quality, mainly due to risk of bias and indirectness. Most studies were at serious or very serious risk of bias, mainly due to issues with patient selection, lack of reporting on conduct/interpretation of the index and reference tests and the time interval between them.*
- *All evidence was considered very indirect due to the lack of a gold standard test for vitamin B12 deficiency, the lack of study reporting on use of vitamin B12 containing supplements and mixed/unclear strata. All evidence was in mixed adult populations, including adults ( $\geq 16/18$  years) and older adults ( $\geq 65$  years), males and females. Ethnicity and pregnancy status was not reported.*
- *Some outcomes were downgraded for serious or very serious imprecision, depending on whether the confidence intervals crossed one or both clinical decision thresholds. **No meta-analysis was performed due to the different index test cut-offs and reference standards used; therefore, inconsistency was not relevant for this review.** The committee considered the limitations of the evidence outlined above and acknowledged the difficulty in drawing any firm conclusions.*

# DIAGNOSING B12 DEFICIENCY

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## DIAGNOSTIC TEST ACCURACY – VERY LOW QUALITY OF EVIDENCE FROM STUDIES

- *Ranges of sensitivities and specificities for the tests recommended by the committee: the sensitivities and specificities of the index tests varied widely within and between studies, depending on the different reference ranges/cut-offs and reference standards used, but no clear pattern emerged. The committee considered the very low quality and the limitations of the diagnostic test accuracy evidence together with the absence of clinical and cost effectiveness evidence and determined that there was insufficient evidence upon which to base recommendations.*
- *The committee agreed that the weak evidence base reflected the difficulties in diagnosis and lack of a single reliable diagnostic test, including the most widely used total B12 assay.*
- *The committee discussed the inadequacies of the total B12 assay as a gold standard test for deficiency. For example, low total B12 concentration does not necessarily indicate deficiency and high concentration does not necessarily exclude deficiency. **In addition, it is not known how vitamin B12 levels in the peripheral blood correlate with levels in the central nervous system.** The committee also highlighted the unmet need of people with borderline total B12 results, who do not receive a diagnosis of deficiency, but may require further testing. In the absence of evidence clearly supporting any single test or combination of tests over another, the committee considered the advantages and disadvantages of the different test options available.*

# DIAGNOSING B12 DEFICIENCY

[HTTPS://WWW.NICE.ORG.UK/GUIDANCE/NG239](https://www.nice.org.uk/guidance/ng239)

## DIAGNOSTIC TEST ACCURACY – VERY LOW QUALITY OF EVIDENCE FROM STUDIES

- *The committee discussed the implications of the timing of diagnostic tests for people with suspected vitamin B12 deficiency.*
- *If blood samples are taken after a person has started treatment, then the test results are unlikely to accurately reflect the person's true vitamin B12 status. Therefore, the committee recommended that blood samples for testing should be taken before treatment is started.*
- *The committee were aware that people may use vitamin B12 supplements, which can contain doses of vitamin B12 between 100 and 2000mcg. **The committee considered that some higher doses could affect or invalidate test results as they can raise levels of vitamin B12 in the body, potentially disguising a deficiency.** The committee discussed whether it would be feasible to delay testing until the effects of the supplement are eliminated. **However, the committee concluded that there are too many variables such as different strengths, durations, preparations and impaired absorption, to be able to accurately determine the correct washout period.** It was therefore recommended that use of supplements should be investigated and taken into consideration when interpreting the results of the test.*

# THRESHOLDS FOR INITIAL TEST RESULTS

[HTTPS://WWW.NICE.ORG.UK/GUIDANCE/NG239](https://www.nice.org.uk/guidance/ng239)

For total or active B12 tests:

- Use the thresholds in table 1 (on next slide) to guide diagnosis **or**
- Where there is substantial local variation in total B12 validated thresholds, use those set by the laboratory doing the testing.

# INTERPRETING TOTAL OR ACTIVE B12 TEST RESULTS

[HTTPS://WWW.NICE.ORG.UK/GUIDANCE/NG239](https://www.nice.org.uk/guidance/ng239)

## RESULTS IF TESTING TOTAL B12 CONCENTRATIONS

- Less than 180 nanograms (133 pmol) per litre
- Between 180 and 350 nanograms (133 and 258 pmol) per litre
- More than 350 nanograms (258 pmol) per litre

## RESULTS IF TESTING ACTIVE B12 CONCENTRATIONS

- Less than 25 pmol per litre
- Between 25 and 70 pmol per litre
- More than 70 pmol per litre

## LIKELIHOOD OF VITAMIN B12 DEFICIENCY

- Confirmed vitamin B12 deficiency
- Indeterminate test result – possible vitamin B12 deficiency
- Test result suggests vitamin B12 deficiency is unlikely

- Use the laboratory's reference ranges to interpret serum MMA test results when deciding if vitamin B12 deficiency is likely.
- Use laboratory reference ranges to interpret plasma homocysteine test results when deciding if vitamin B12 deficiency is likely, but take into account additional factors that may increase plasma homocysteine levels (such as folate deficiency).

# WHEN RESULTS ARE INDETERMINATE OR SUGGEST DEFICIENCY IS UNLIKELY

[HTTPS://WWW.NICE.ORG.UK/GUIDANCE/NG239](https://www.nice.org.uk/guidance/ng239)

Consider a further test to measure serum MMA concentrations in people who have symptoms or signs of vitamin B12 deficiency and an indeterminate total or active B12 test result.

***Be aware that people of Black ethnicity may have a higher reference range for serum vitamin B12 concentrations than people of White or Asian ethnicity.***

Consider vitamin B12 replacement for people who have an initial test result that is indeterminate (see table 1) and meet any of the following criteria:

- They have a condition or symptom that may deteriorate rapidly and have a major effect on quality of life (for example, neurological or haematological conditions such as ataxia or anaemia)
- They have a condition or suspected condition that is an irreversible cause of vitamin B12 deficiency (for example, autoimmune gastritis)



# WHEN RESULTS ARE INDETERMINATE OR SUGGEST DEFICIENCY IS UNLIKELY

[HTTPS://WWW.NICE.ORG.UK/GUIDANCE/NG239](https://www.nice.org.uk/guidance/ng239)

- They have had surgery that can cause vitamin B12 deficiency (such as a gastrectomy, terminal ileal resection or some types of bariatric surgery)
- They are pregnant or breastfeeding.

If also carrying out a further test to measure serum MMA concentrations, start vitamin B12 replacement while waiting for this test result.

# WHEN RESULTS ARE INDETERMINATE OR SUGGEST DEFICIENCY IS UNLIKELY

[HTTPS://WWW.NICE.ORG.UK/GUIDANCE/NG239](https://www.nice.org.uk/guidance/ng239)

Advise people with no symptoms or signs of vitamin B12 deficiency and an indeterminate total or active B12 test result (see table 1) to seek medical help if they develop symptoms or signs of deficiency.

If the person's initial test result suggests vitamin B12 deficiency is unlikely :

- Investigate other causes of their symptoms and
- ***If they are still experiencing symptoms 3 to 6 months later, consider a repeat of the initial test.***

# WHEN RESULTS ARE INDETERMINATE OR SUGGEST DEFICIENCY IS UNLIKELY

[HTTPS://WWW.NICE.ORG.UK/GUIDANCE/NG239](https://www.nice.org.uk/guidance/ng239)

Note:

- **The committee noted that there is currently no 'gold standard' test for diagnosing vitamin B12 deficiency. This means that while tests can be a diagnostic aid, they cannot be completely relied on to confirm or rule out deficiency (for example, a person with an indeterminate test result could still have a deficiency).**
- *In the absence of evidence, the committee used their experience and expertise to define clear thresholds for test results. These will help healthcare professionals decide when to diagnose deficiency and what to do if results are indeterminate or suggest deficiency is unlikely.*
- **There are no generally accepted reference ranges for serum MMA and plasma homocysteine testing.**
- *Recent evidence from large cohort studies, based on samples that are representative of the UK population, suggests that people of Black ethnicity may have a higher reference range for serum concentrations of vitamin B12 in their blood than people of White or Asian ethnicity. However, the same reference range is currently used for people of all ethnicity. **This means people of Black ethnicity may need treatment even if their blood test results are above one of the cut-offs used in the guideline to determine vitamin B12 deficiency. This will need to be taken into account together with symptoms, signs and risk factors when interpreting test results.***

# FACTORS INFLUENCING THE ACCURACY OF RESULTS OF SERUM B12 AND RELATED BIOMARKERS

[HTTPS://WWW.BMJ.COM/CONTENT/383/BMJ-2022-071725](https://www.bmj.com/content/383/bmj-2022-071725)

(VITAMIN B12 (PRACTICE THERAPEUTICS PUBLISHED 20 NOVEMBER 2023))

- Considerable variability exists between the different commercially available serum B12 assays.
- Day-to-day variation of serum B12 may occur; for example, a concentration of 150 pmol/L on one day may be 120 pmol/L another day.
- ***A serum B12 concentration within the normal limit, i.e, above 148 pmol/l, does not exclude deficiency.***
- ***Serum B12 concentrations may be influenced by specific genetic polymorphisms or mutations; currently, more than 15 single nucleotide polymorphisms are known to influence serum B12.***
- Oral B12 supplementation may result in serum B12 concentrations within or sometimes above the “normal” range without reducing symptoms, which can obscure the correct diagnosis.
- Holo-transcobalamin (holoTC-active B12), the biologically active form of vitamin B12 in blood, also has a wide window with indeterminate levels, and the reference values strongly depend on the assay method.
- Measuring serum concentrations of MMA and homocysteine may be helpful in establishing B12 deficiency, especially in people with borderline serum B12 levels, i.e, those between 148 and 300 pmol/L. ***However, MMA was normal in 52% of individuals with holoTC concentrations below 20 pmol/L, the latter being indicative of deficiency.*** Additionally, specific genetic polymorphisms and recent treatment with antibiotics may result in false normal MMA levels, and MMA is also elevated with impaired renal function.
- ***Serum homocysteine is less specific for B12 deficiency, and can also be elevated in folate deficiency, vitamin B6 deficiency, vitamin B2 deficiency, and impaired renal function, hypothyroidism, and by certain medications.***

# FACTORS INFLUENCING THE ACCURACY OF RESULTS OF SERUM B12 AND RELATED BIOMARKERS

[HTTPS://WWW.BMJ.COM/CONTENT/383/BMJ-2022-071725](https://www.bmj.com/content/383/bmj-2022-071725)

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*Additionally, in patients who are already taking some form of oral B12 supplementation, demonstrating B12 deficiency can be a challenge, even when symptoms are typical (including those of neuropathy-like paraesthesia and numbness) as serum B12 concentrations may be just within, or sometimes above, the “normal” range.*

*Serum B12, homocysteine, and Methylmalonic acid (MMA) levels are unreliable predictors of B12 responsive neuropathy (neurological disorders that respond to B12 supplementation).*

*In these situations, **expert opinion suggests that clinicians consider discussing with their patients a therapeutic trial of B12 injections.***

# IDENTIFYING THE CAUSE OF VITAMIN B12 DEFICIENCY

[HTTPS://WWW.NICE.ORG.UK/GUIDANCE/NG239](https://www.nice.org.uk/guidance/ng239)

Consider an anti-intrinsic factor antibody test for people with vitamin B12 deficiency if autoimmune gastritis is suspected and they have not previously had:

- A positive anti-intrinsic factor antibody test at any time **or**
- An operation that could affect vitamin B12 absorption (such as total gastrectomy or complete terminal ileal resection).

If vitamin B12 deficiency is diagnosed in pregnancy or during breastfeeding and autoimmune gastritis is the suspected cause:

- Offer an anti-intrinsic factor antibody test if the criteria in recommendation 1.4.1 is met **and**
- Start treatment with intramuscular vitamin B12 replacement without waiting for the test result.

When interpreting anti-intrinsic factor antibody test results:

- Follow the guidance provided by the laboratory doing the test **and**
- ***Be aware that a negative test result does not rule out the presence of autoimmune gastritis.***

# IDENTIFYING THE CAUSE OF VITAMIN B12 DEFICIENCY

[HTTPS://WWW.NICE.ORG.UK/GUIDANCE/NG239](https://www.nice.org.uk/guidance/ng239)

Laboratories should provide information on what their anti-intrinsic factor antibody assay detects and how to interpret results.

If autoimmune gastritis is still suspected despite a negative anti-intrinsic factor antibody test, consider further investigations such as:

- An anti-gastric parietal cell antibody test
- A test to measure gastrin levels
- A Cobasorb test to measure whether vitamin B12 can be absorbed
- Gastroscopy with gastric body biopsy (to be carried out by a specialist).

Offer serological testing for coeliac disease where the cause of vitamin B12 deficiency is still unknown after further investigations

# IDENTIFYING THE CAUSE OF VITAMIN B12 DEFICIENCY

[HTTPS://WWW.NICE.ORG.UK/GUIDANCE/NG239](https://www.nice.org.uk/guidance/ng239)

Note:

- *The committee agreed it was important to test people if they have suspected autoimmune gastritis because this is an irreversible condition and they will need lifelong vitamin B12 replacement. Evidence found the anti-intrinsic factor antibody test to be the best initial option for diagnosing autoimmune gastritis.*
- ***The evidence also showed that, while a positive anti-intrinsic factor antibody test strongly suggests autoimmune gastritis, a negative test is less reliable so cannot be used to rule out the condition. Therefore, some people may need further investigations. Based on their experience and expertise, the committee agreed to a list of some options for this but there was insufficient evidence to recommend one investigation over the other.***
- *The choice would also depend on availability of the investigation and whether there were suitably trained and skilled healthcare staff available to carry it out. Gastroscopy can only be carried out by a specialist.*
- ***The committee also acknowledged that this procedure, if it included a gastric body biopsy, would normally determine if someone had autoimmune gastritis. However, it is also an invasive and expensive procedure. The committee also acknowledged that none of the other tests listed in the recommendation can completely rule out autoimmune gastritis.***



# TESTS TO DETERMINE AETIOLOGY OF B12 DEFICIENCY: INTRINSIC FACTOR ANTIBODIES

[HTTPS://ONLINELIBRARY.WILEY.COM/DOI/FULL/10.1111/BJH.12959](https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.12959)

(Guidelines for the diagnosis and treatment of cobalamin and folate disorders – British Journal of Haematology 2014)

- Pernicious Anaemia (PA) is characteristically diagnosed by the presence of intrinsic factor antibodies. A low serum B12 level can be further evaluated with this test.
- It is **highly specific** with a high positive predictive value of 95% for the presence of Pernicious Anaemia. It identifies those who will need lifelong B12 replacement.
- However, it is only positive in 40-60% of cases (**low sensitivity**). **A negative intrinsic factor antibody test, therefore, does not rule out Pernicious Anaemia.**
- Positivity of the test increases with age and in certain racial groups (Latino-Americans and African-Americans)
- **High titre IF antibody may interfere with serum B12 assays leading to false normal serum B12 levels.**
- **Testing for IF antibodies is therefore advised in patients with strong clinical features of deficiency DESPITE normal serum B12 level.** In these cases, pre-treatment serum should be stored for investigation with an alternate test such as MMA.

# TESTS TO DETERMINE AETIOLOGY OF B12 DEFICIENCY: GASTRIC PARIETAL CELL ANTIBODIES

[HTTPS://ONLINELIBRARY.WILEY.COM/DOI/FULL/10.1111/BJH.12959](https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.12959)

(Guidelines for the diagnosis and treatment of cobalamin and folate disorders – British Journal of Haematology 2014)

- Positive in 80% of people with Pernicious Anaemia, so **high sensitivity** .. that means if it is negative it is likely the patient does not have Pernicious Anaemia, although not impossible.
- ***Most patients with Pernicious Anaemia have positive parietal cell antibodies but not all patients with positive parietal cell antibodies have Pernicious Anaemia***
- The test is also positive in 10% of normal individuals and in other conditions such as hypothyroidism.
- The British Society of Haematology 2014 guidelines do not recommend it as a diagnostic test due to its **low specificity**.

# TESTS TO DETERMINE AETIOLOGY OF B12 DEFICIENCY: SCHILLING TEST

[HTTPS://ONLINELIBRARY.WILEY.COM/DOI/FULL/10.1111/BJH.12959](https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.12959)

(Guidelines for the diagnosis and treatment of cobalamin and folate disorders – British Journal of Haematology 2014)

- No longer performed. Expensive and difficult to source radioactive-labelled B12.
- In the past patients with negative intrinsic factor antibodies and low serum B12 levels would have had this test.
- It provided objective evidence of vitamin B12 malabsorption using radioactively labelled B12 (part 1) and evidence of whether this was corrected with the addition of intrinsic factor (part 2)
- A new vitamin B<sub>12</sub> absorption test, CobaSorb, was introduced nearly 10 years ago. CobaSorb is based on oral intake of non-radioactive vitamin B<sub>12</sub> followed by measurement of an increase in holotranscobalamin (holoTC) 24 hours later.

<https://ashpublications.org/blood/article/108/11/3749/126834/CobaSorb-a-New-Non-Radioactive-Vitamin-B12> (Published November 2006)

# MANAGING VITAMIN B12 DEFICIENCY

[HTTPS://WWW.NICE.ORG.UK/GUIDANCE/NG239](https://www.nice.org.uk/guidance/ng239)

Explain to people starting treatment with vitamin B12 replacement:

- That response to treatment can vary and depends on the cause of the vitamin B12 deficiency
- That their symptoms could start to improve within 2 weeks, but this may take up to 3 months
- ***That it can take much longer for symptoms to disappear altogether, and that although their symptoms could get worse initially during treatment, this should improve***
- When to seek medical help (without waiting for any scheduled appointments) if their symptoms have not improved, get worse or return, or they get new symptoms, after starting treatment.

Continue with vitamin B12 replacement if treatment was started before pregnancy or breastfeeding and review this treatment at a later date.

# MANAGING VITAMIN B12 DEFICIENCY

[HTTPS://WWW.NICE.ORG.UK/GUIDANCE/NG239](https://www.nice.org.uk/guidance/ng239)

EVIDENCE BASE

- *The committee considered quality of life, patient reported outcomes including symptom scores, haematological values, complications and adverse events, adherence to treatment and education/work absence to be the most important outcomes of vitamin B12 replacement.*
- *The majority of the evidence for vitamin B12 replacement identified from randomised controlled trials was for haematological values, with very little evidence identified for patient reported outcomes. No evidence was identified for quality of life, adherence to treatment, or education/work absence. The committee considered that although haematological values provide useful objective biomarkers, the end purpose of B12 replacement is to improve the patients' quality of life, **so the RCT evidence was not considered sufficient upon which to base recommendations.***
- *Therefore, a search for observational evidence was carried out. However, the evidence identified from observational studies was for haematological values only.*
- *Evidence ranged from **moderate to very low-quality, with the majority of evidence being assessed as very low-quality.** Indirectness was the main reason for downgrading, with almost all evidence being downgraded by one increment due to the inclusion of populations with mixed causes of vitamin B12 deficiency.*

# MANAGING VITAMIN B12 DEFICIENCY

[HTTPS://WWW.NICE.ORG.UK/GUIDANCE/NG239](https://www.nice.org.uk/guidance/ng239)  
EVIDENCE BASE

- Overall, the committee felt that the evidence identified **was of limited use in the decision making process.**
- **The small number of studies identified for each comparator was a particularly limiting factor, with no meta-analyses possible across the review.**
- Compounding the difficulty in interpreting the results was the significant differences in populations and interventions used in the identified studies. **Only one study included participants with a single cause of vitamin B12 deficiency, with all others including people with a number of different causes.**
- Furthermore, studies utilised a number of different definitions of deficiency and doses, frequencies and durations of treatment. **These factors made it difficult to compare across studies and to draw conclusions from the evidence as a whole.**

# MALABSORPTION AS THE CONFIRMED OR SUSPECTED CAUSE OF VITAMIN B12 DEFICIENCY

[HTTPS://WWW.NICE.ORG.UK/GUIDANCE/NG239](https://www.nice.org.uk/guidance/ng239)

Offer lifelong intramuscular vitamin B12 replacement to people if:

- Autoimmune gastritis is the cause, or suspected cause, of vitamin B12 deficiency **or**
- They have had a total gastrectomy, or a complete terminal ileal resection.

If the person has a vitamin B12 deficiency because of malabsorption that is not caused by autoimmune gastritis, or a total gastrectomy or complete terminal ileal resection (for example, malabsorption caused by coeliac disease, partial gastrectomy or some forms of bariatric surgery):

- Offer vitamin B12 replacement **and**
- Consider intramuscular instead of oral vitamin B12 replacement.

***When offering oral vitamin B12 replacement to people with vitamin B12 deficiency caused, or suspected to be caused, by malabsorption, prescribe a dosage of at least 1 mg (1000mcg) a day.***

# MEDICINE-INDUCED VITAMIN B12 DEFICIENCY

[HTTPS://WWW.NICE.ORG.UK/GUIDANCE/NG239](https://www.nice.org.uk/guidance/ng239)

For people with vitamin B12 deficiency that is a side effect of taking a medicine:

- Offer either intramuscular or oral vitamin B12 replacement, based on clinical judgement and the person's preference, while they are taking the medicine causing the side effect, **and**
- If appropriate, review use of the medicine that is causing the side effect to see if it is still needed or can be changed.

Review the need for vitamin B12 replacement if the medicine causing the side effect is stopped or changed and the person no longer has symptoms of vitamin B12 deficiency.



# RECREATIONAL NITROUS OXIDE USE AS THE CAUSE OF VITAMIN B12 DEFICIENCY

[HTTPS://WWW.NICE.ORG.UK/GUIDANCE/NG239](https://www.nice.org.uk/guidance/ng239)

- Offer either intramuscular or oral vitamin B12 replacement to people with a vitamin B12 deficiency caused by recreational nitrous oxide use, based on clinical judgement and the person's preference.
- Advise the person to stop using nitrous oxide recreationally.
- Review the need for vitamin B12 replacement if the person stops using nitrous oxide recreationally and they no longer have symptoms of vitamin B12 deficiency.
- *Recreational nitrous oxide is known to cause vitamin B12 deficiency by inactivating the vitamin in the body, but its longer-term effects are unknown. There was no evidence to suggest either oral or intramuscular vitamin B12 replacement was a better treatment for deficiency of this cause, so the committee agreed that either should be offered, depending on clinical judgement and the person's preference. They also agreed that people should be advised to stop using nitrous oxide recreationally to prevent the deficiency from getting worse.*

# RECREATIONAL NITROUS OXIDE USE AS THE CAUSE OF VITAMIN B12 DEFICIENCY

[HTTPS://WWW.NICE.ORG.UK/GUIDANCE/NG239](https://www.nice.org.uk/guidance/ng239)

- *The committee agreed that, if the person stops using nitrous oxide recreationally and they no longer have symptoms of vitamin B12 deficiency, the need for vitamin B12 replacement should be reviewed. This is because the cause of deficiency would have been removed.*
- *However, the person may need to continue with vitamin B12 replacement even after they have stopped using nitrous oxide, because it is unclear how long it will take for the deficiency to fully resolve.*

# DIETARY VITAMIN B12 DEFICIENCY

[HTTPS://WWW.NICE.ORG.UK/GUIDANCE/NG239](https://www.nice.org.uk/guidance/ng239)

If the person has vitamin B12 deficiency where diet is the suspected cause:

- Enquire about diet and whether they are taking any OTC supplements
- Check whether they have any symptoms, signs or risk factors that could suggest another cause of vitamin B12 deficiency
- Be aware that diet (for example, a vegetarian or vegan diet) may not be the cause, or the only cause, of a person's vitamin B12 deficiency.
- Consider further investigations to explore other causes of vitamin B12 deficiency if, during discussions, the person suggests or gives information that raises suspicion that the deficiency is not linked to their diet

# DIETARY VITAMIN B12 DEFICIENCY

[HTTPS://WWW.NICE.ORG.UK/GUIDANCE/NG239](https://www.nice.org.uk/guidance/ng239)

If the person is taking, or plans to take, over-the-counter oral supplements that contain vitamin B12:

- Explain that some supplements do not contain enough, or the right type, of vitamin b12 to be effective and
- Advise them to pick an oral supplement that contains at least 1 of the following types of vitamin b12:
  - Cyanocobalamin
  - Methylcobalamin
  - Adenosylcobalamin.

# DIETARY VITAMIN B12 DEFICIENCY

[HTTPS://WWW.NICE.ORG.UK/GUIDANCE/NG239](https://www.nice.org.uk/guidance/ng239)

If the person has suspected or confirmed vitamin B12 deficiency because their diet is lacking in vitamin B12:

- Tell them where to find information on how to improve their intake of vitamin B12, including information about sources in food **and**
- Consider oral vitamin B12 replacement.

***When offering oral vitamin B12 replacement in pregnancy or during breastfeeding, consider a dosage of at least 1 mg (1000mcg) a day.***

Consider intramuscular vitamin B12 injections instead of oral replacement for suspected or confirmed vitamin b12 deficiency caused by diet if:

- The person has another condition that may deteriorate rapidly and have a major effect on their quality of life (for example, a neurological or haematological condition such as ataxia or anaemia)
- There are concerns about adherence to oral treatment, for example, if the person:
  - Is older, is or has recently been in hospital and has either multi-morbidity or frailty
  - Has delirium or cognitive impairment
  - Is affected by social issues that may prevent them accessing care, such as homelessness.

# UNKNOWN CAUSES OF VITAMIN B12 DEFICIENCY

[HTTPS://WWW.NICE.ORG.UK/GUIDANCE/NG239](https://www.nice.org.uk/guidance/ng239)

In people with a vitamin B12 deficiency where the cause is uncertain, and malabsorption is not suspected based on the results of further testing or investigations:

- Offer vitamin B12 replacement **and**
- Consider oral instead of intramuscular vitamin B12 replacement and review response to treatment at the person's first follow-up appointment.

# ORAL CYANOCOBALAMIN

[BNF.NICE.ORG.UK/DRUGS/CYANOCOBALAMIN/](http://BNF.NICE.ORG.UK/DRUGS/CYANOCOBALAMIN/)

## INDICATIONS AND DOSE FOR ADULTS

**Dietary vitamin B12 deficiency** 50–150 micrograms once daily, dose to be taken between meals, dose may be increased as clinically indicated.

**Dietary vitamin B12 deficiency during pregnancy or breast feeding** 1 mg once daily, dose to be taken between meals, dose may be increased as clinically indicated.

**Dietary vitamin B<sub>12</sub> deficiency or vitamin B<sub>12</sub> deficiency due to malabsorption**

### **Orbalin – 1mg cyanocobalamin film-coated tablets**

Initially 2 mg twice daily until remission, dose to be taken between meals, then maintenance 1 mg once daily, dose to be taken between meals.

# HYDROXOCOBALAMIN

[HTTPS://BNF.NICE.ORG.UK/DRUGS/HYDROXOCOBALAMIN/](https://bnf.nice.org.uk/drugs/hydroxocobalamin/)

## INDICATIONS AND DOSE FOR ADULTS BY INTRAMUSCULAR INJECTION

**Prophylaxis of macrocytic anaemias associated with vitamin B12 deficiency** 1 mg every 2–3 months.

**Pernicious anaemia and other macrocytic anaemias WITHOUT neurological involvement** Initially 1 mg 3 times a week for 2 weeks, then 1 mg every 2–3 months.

**Pernicious anaemia and other macrocytic anaemias WITH neurological involvement** Initially 1 mg once daily on alternate days until no further improvement, then 1 mg every 2 months.

**Tobacco amblyopia** Initially 1 mg daily for 2 weeks, then 1 mg twice weekly until no further improvement, then 1 mg every 1–3 months.

**Leber's optic atrophy** Initially 1 mg daily for 2 weeks, then 1 mg twice weekly until no further improvement, then 1 mg every 1–3 months.

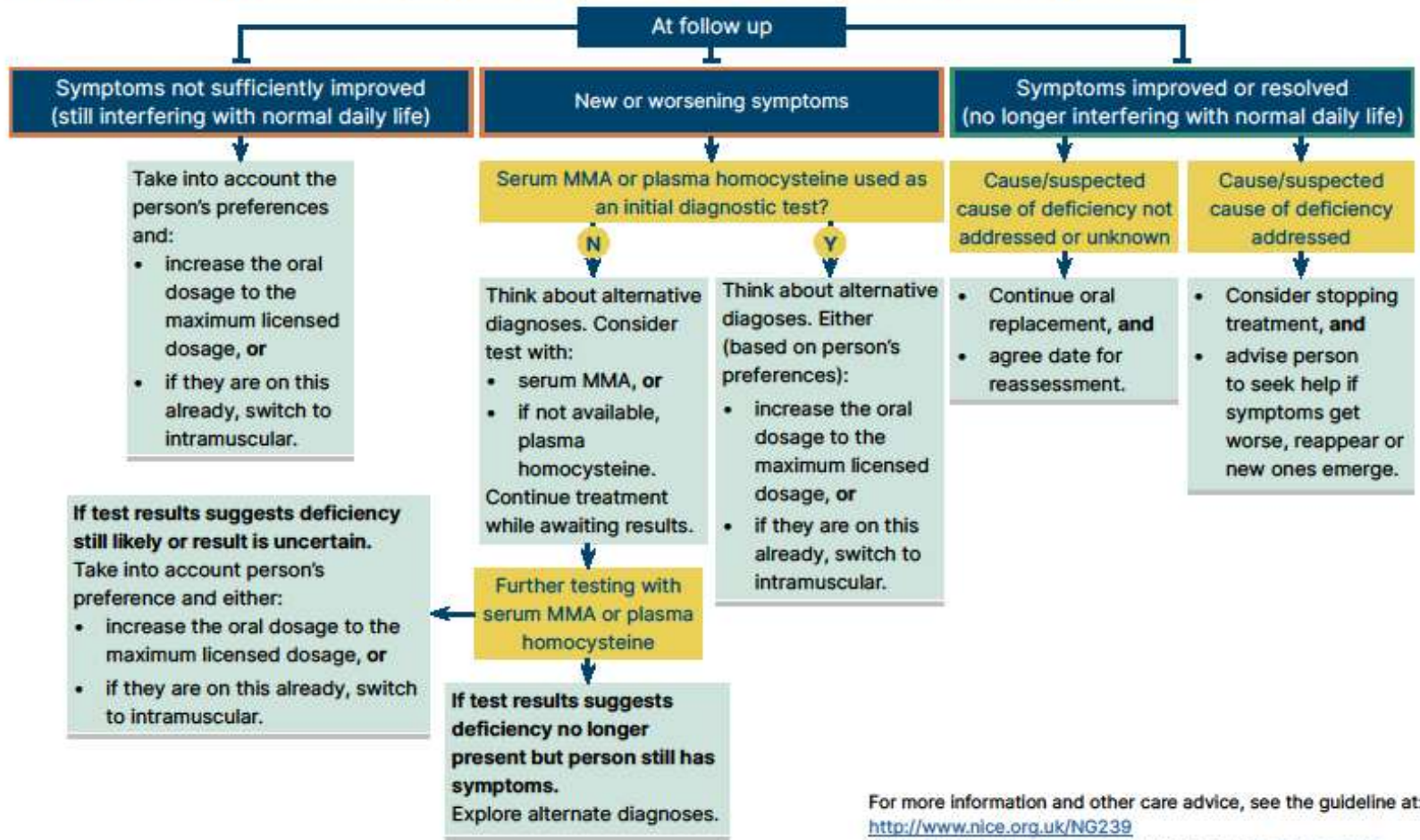


# IMPORTANT SAFETY INFORMATION

## MHRA/CHM ADVICE: VITAMIN B12 (HYDROXOCOBALAMIN AND CYANOCOBALAMIN): ADVISE PATIENTS WITH KNOWN COBALT ALLERGY TO BE VIGILANT FOR SENSITIVITY REACTIONS (DECEMBER 2023)

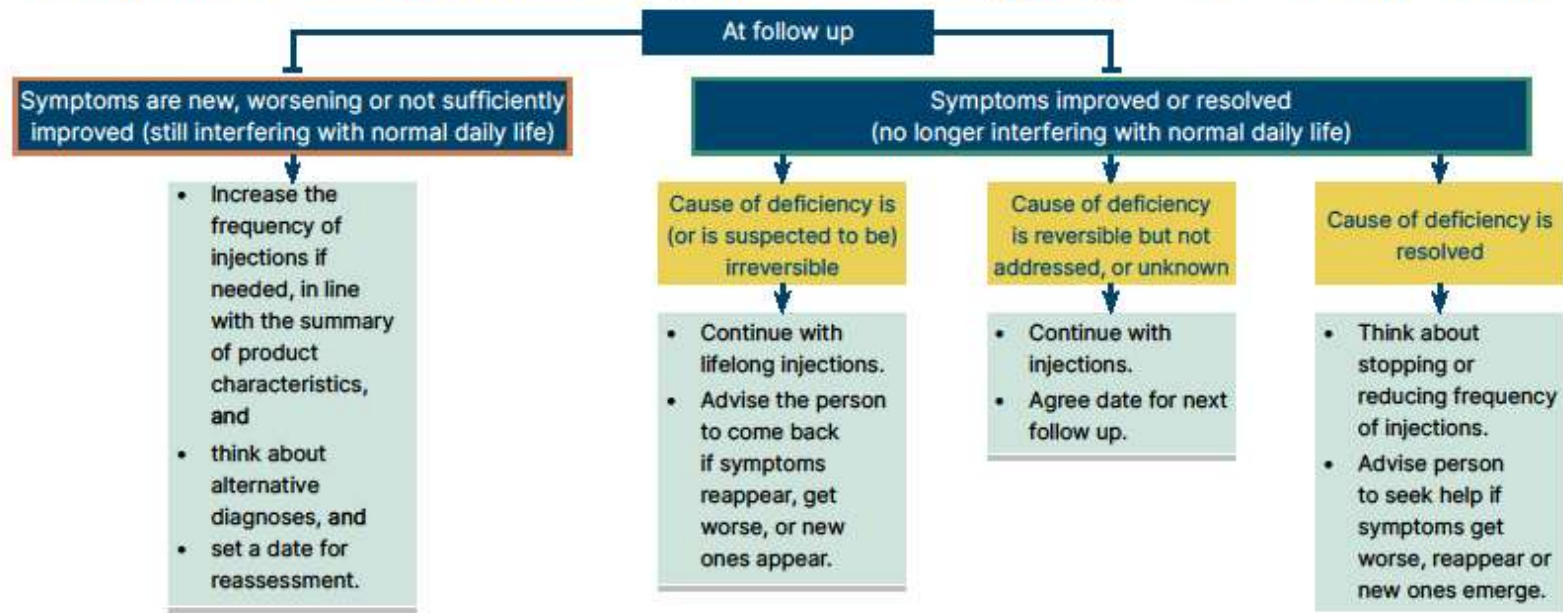
- Following a report via the yellow card scheme, the MHRA conducted a review and found evidence in the literature of cobalt sensitivity-type reactions in patients being treated for vitamin B12 deficiency; other similar reports have also been received. ***Such reactions typically present with cutaneous symptoms of chronic or subacute allergic contact dermatitis (an erythema multiforme-like eruption may infrequently be triggered); onset may be immediate or delayed up to 72 hours after vitamin B12 administration.*** Vitamin B12 (i.e. Cyanocobalamin or hydroxocobalamin) contains cobalt and 1 to 3% of the general population is estimated to have cobalt allergy.
- Healthcare professionals are recommended to assess the benefits and risks of continuing treatment in patients who develop cobalt sensitivity-type reactions and, if necessary to continue, advise such patients on appropriate symptom management. Patients with known cobalt allergy should be advised to speak to a healthcare professional if they are prescribed vitamin B12 and be alert for symptoms of cobalt sensitivity-type reactions. All patients should be counselled to seek medical advice if they develop allergic skin reactions whilst on vitamin B12 therapy; urgent medical attention must be sought if symptoms of a serious allergic reaction, such as extensive or blistering rash, wheeze, difficulty breathing, or feeling faint, occur.
- ***Hydroxocobalamin preparations used for the treatment of known or suspected cyanide poisoning are excluded from these precautions because the potentially life-saving benefit of treatment in a medical emergency outweighs the risk of an allergic reaction.***

# Oral vitamin B12 replacement: ongoing care and follow up



For more information and other care advice, see the guideline at: <http://www.nice.org.uk/NG239>  
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 Last updated March 2024. ISBN 978-1-4731-5728-6.

# Intramuscular vitamin B12 replacement: ongoing care and follow up



For more information and other care advice, see the guideline at:

<http://www.nice.org.uk/NG239>

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Last updated March 2024. ISBN 978-1-4731-5728-6.

# MONITORING FOR GASTRIC CANCER IN PEOPLE WITH SUSPECTED OR CONFIRMED AUTOIMMUNE GASTRITIS

[HTTPS://WWW.NICE.ORG.UK/GUIDANCE/NG239](https://www.nice.org.uk/guidance/ng239)

At follow up, take into account that people who have autoimmune gastritis:

- Are at higher risk of developing gastric neuroendocrine tumours **and**
- May also be at higher risk of developing gastric adenocarcinoma.

If the person has suspected or confirmed autoimmune gastritis and new, or worsening, upper gastrointestinal symptoms (for example, dyspepsia, nausea or vomiting):

- Consider referral for a gastrointestinal endoscopy **and**
- Follow the recommendations on upper gastrointestinal tract cancers in NICE's guideline on suspected cancer.

# COMMON MISTAKES IN CLINICAL PRACTICE

1. Not testing for B12 deficiency due to lack of awareness of possible signs and symptoms of deficiency – especially those that are not seen commonly.

2. Not testing for B12 deficiency in people who do not have ANAEMIA or MACROCYTOSIS despite symptoms and signs of B12 deficiency and/or risk factors being present.

*There is a common misconception that a person cannot have B12 deficiency unless either or both of these signs are present.*

*Absence of a raised MCV cannot be used to exclude the need for B12 testing because neurological impairment occurs with a normal MCV in 25% of cases (British Journal Haematology 2014*

*[HTTPS://ONLINELIBRARY.WILEY.COM/DOI/FULL/10.1111/BJH.12959](https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.12959) )*

# COMMON MISTAKES IN CLINICAL PRACTICE

3. Over-reliance on diagnostic tests and dismissing B12 deficiency prematurely based on normal test results, despite clinical features in keeping with the diagnosis due to lack of awareness of limitations of tests and evidence base.

<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3827408/> Undetected vitamin B12 deficiency due to false normal assay results – case report published Oct 2013.

*Patient had macrocytic anaemia and other features of B12 deficiency but raised B12 level > 900 so was not treated initially despite Parietal and intrinsic factor antibodies being strongly positive. Repeat tests from another lab were in low normal range. Patient was treated with B12 replacement. After 2 weeks the patient's condition improved and complete clinical and haematological recovery occurred within the next month*

4. Ruling out Pernicious Anaemia based on a negative anti-intrinsic factor antibody result.

*The test has a low specificity and so a negative value CANNOT exclude Pernicious Anaemia.*

# COMMON MISTAKES IN CLINICAL PRACTICE

5. Ruling out B12 deficiency despite clinical signs and symptoms based on a “normal” serum B12 level.

*There is no international consensus regarding reference ranges to define B12 deficiency. The UK reference ranges are much lower than in other countries. In Japan, the lower limit of normal is set at 500ng/l compared to around 200ng/l in UK labs.*

6. Not considering the possibility of B12 deficiency as a cause of symptoms in patients who are already taking oral supplements or having intramuscular B12 injections.

*Oral supplements may not sufficiently treat deficiency and so patients could become symptomatic. Injection frequency may need to be increased in some people.*

7. Considering serum B12 levels as an accurate measure of B12 stores in those taking OTC supplements

*Oral supplements can affect the B12 assay resulting in a normal or raised value despite the patient having deficiency related symptoms.*

# COMMON MISTAKES IN CLINICAL PRACTICE

8. Not considering the possibility of **FUNCTIONAL B12 DEFICIENCY** in those with normal or raised serum B12 levels despite clinical features of B12 deficiency being present.

<https://www.ejgm.co.uk/article/vitamin-b12-deficiency-some-observations-some-misconceptions-7272>

EUR J GEN MED, Volume 12, Issue 3, July 2015, 261-266 – Article on Functional B12 deficiency

<https://www.bmj.com/content/376/bmj-2021-068243.r2> BMJ Case Review - A teenage girl with knuckle hyperpigmentation published February 2022

*The patient had developed knuckle hyperpigmentation and progressive fatigue over the past month. She was vegetarian. Initial tests showed raised B12 levels and low ferritin. A homocysteine level was raised with normal folate indicating functional B12 deficiency caused by reduced tissue stores of B12 (i.e. B12 not being transported from serum into the cells). The patient responded to B12 replacement with skin pigmentation resolution and her fatigue resolving also.*



# COMMON MISTAKES IN CLINICAL PRACTICE

9. Testing serum B12 after starting B12 injections and stopping treatment based on normalisation/ raised B12 levels.

10. Stopping B12 injections or switching to oral supplements due to negative intrinsic factor antibody.

*A negative IF antibody result does not rule out Pernicious Anaemia.*

11. Considering high dose oral B12 supplementation as equivalent to Intramuscular B12 injections based on very low quality or low quality evidence.

**Inherited and acquired vitamin B12 deficiencies: which administration route to choose for supplementation? Published September 2022**

<https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2022.972468/full>

# COMMON MISTAKES IN CLINICAL PRACTICE

**Oral vitamin B<sub>12</sub> versus intramuscular vitamin B<sub>12</sub> for vitamin B<sub>12</sub> deficiency – Cochrane Review 2018 (most up to date)**<https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD004655.pub3/full>

*Conclusion:*

*“Low quality evidence shows oral and IM vitamin B<sub>12</sub> having similar effects in terms of normalising serum vitamin B<sub>12</sub> levels, but oral treatment costs less. **We found very low-quality evidence that oral vitamin B<sub>12</sub> appears as safe as IM vitamin B<sub>12</sub>.** Further trials should conduct better randomisation and blinding procedures, recruit more participants, and provide adequate reporting. Future trials should also measure important outcomes such as the clinical signs and symptoms of vitamin B<sub>12</sub> deficiency, health related-quality of life, socioeconomic effects, and report adverse events adequately, preferably in a primary care setting.”*

*Note only 3 RCT met their criteria. Only 153 participants – so low numbers.*

# COMMON MISTAKES IN CLINICAL PRACTICE

**Efficacy of different routes of vitamin B12 supplementation for the treatment of patients with vitamin B12 deficiency: A systematic review and network meta-analysis. Published January 2024**

[HTTPS://LINK.SPRINGER.COM/ARTICLE/10.1007/S11845-023-03602-4](https://link.springer.com/article/10.1007/s11845-023-03602-4)

*Thirteen studies were included in the meta-analysis, with a total of 4275 patients.*

## **Conclusion**

*“All IM, oral, and SL routes of administration of vitamin B12 can effectively increase the level of vitamin B12 without significant differences between them, as thought previously. However, the IM route was the top-ranked statistically but without clinical significance.”*

## **NOTE STUDY FOCUSES ON INCREASE IN SERUM B12 NOT SYMPTOM IMPROVEMENT.**

*“The limitations of this work are that we included RCTs, non-RCTs, and observational studies, which may lower the overall quality of evidence of the included studies. We cannot find the full text of one study which seems to be included. The head-by-head comparison between the three interventions was made only in one paper of the included studies. Additionally, there was variability between the included studies in the follow-up duration, which may cause heterogeneity in the results obtained.”*

# COMMON MISTAKES IN CLINICAL PRACTICE

**Issues to be aware of when interpreting the evidence base that states IM and oral B12 replacement is equivalent:**

Studies comparing Oral vs IM B12 injections have only looked at serum B12 levels, not at response of symptoms.

Many studies have included either people with mainly dietary deficiency or with very few or no symptoms.

Small numbers of participants in most of the studies

Varying definitions of B12 deficiency due to no consensus regarding normal reference ranges

Most studies have conducted a short follow up period of 1-2 months only, although one did follow up patients for a year.

**Serum and cerebrospinal fluid vitamin B12 levels in demented patients with CH3-B12 treatment-- preliminary study** <https://pubmed.ncbi.nlm.nih.gov/3398357/> Published 1988

*Showed virtually no increase in CSF B12 with high dose oral B12 supplementation but significant increase with the addition of IM B12 injections.*

# COMMON MISTAKES IN CLINICAL PRACTICE

## 12. Considering Methylmalonic acid a highly sensitive test

**Association of vitamin B12, Methylmalonic acid, and functional parameters. Published February 2020**

<https://pubmed.ncbi.nlm.nih.gov/32043474/>

Data included 9645 participants

*A large proportion of individuals with a decreased serum B12 concentration still have normal MMA concentrations. Elevated MMA concentrations were more strongly associated with poor functional performance than serum B12.*

*MMA concentrations were elevated in only 56% of people with serum B12 concentrations < 140 pmol/l, and in 13.5% of people with serum B12 in the grey zone of 140-300 pmol/l.*

# COMMON MISTAKES IN CLINICAL PRACTICE

13. Failure to consider diagnosis of B12 deficiency in patients with neurological symptoms but normal total and active serum B12, MMA and antibodies.

**TRANSCOBALAMIN RECEPTOR AUTOANTIBODIES IN CENTRAL VITAMIN B12 DEFICIENCY – PRE-PRINT  
PUBLISHED AUGUST 2023**

<https://www.medrxiv.org/content/10.1101/2023.08.21.23294253v1.full>

*Patient in her 60s with progressive ataxia and tremor – found to have anti-CD320 antibodies and low CSF B12 levels. The antibodies impair transport across the blood-brain barrier and thus patients can manifest with neurological symptoms with normal serum blood tests. Patient's symptoms improved with B12 replacement.*

# COMMON MISTAKES IN CLINICAL PRACTICE

14. Reluctance to increase frequency of maintenance dose B12 injections beyond BNF guidance even when patient is symptomatic.

15. Lack of awareness of signs and symptoms in keeping with Subacute Combined Degeneration of Spinal Cord thus missing the diagnosis altogether leading to increased morbidity and unnecessary investigations.

**Rapid healing of a patient with dramatic subacute combined degeneration of spinal cord: a case report  
Published 2017.**

<https://bmccresnotes.biomedcentral.com/articles/10.1186/s13104-016-2344-4>

**Subacute combined degeneration of the spinal cord (archive). Published March 2024.**

<https://www.ncbi.nlm.nih.gov/books/NBK559316/>

# KEY MESSAGES

- Be aware of the wide variety of symptoms and signs that could indicate B12 deficiency.
- The clinical picture is the most important factor in assessing the significance of results of blood tests assessing cobalamin (B<sub>12</sub>) status because there is no “gold standard” test to define deficiency.
- If there is discordance between test results and clinical features, consider a trial of treatment with B12 before dismissing the diagnosis.
- Be aware that people of Black ethnicity may have a higher reference range for serum vitamin B12 concentrations than people of White or Asian ethnicity.
- Neurological symptoms resulting from B12 deficiency may take several months or even years to resolve completely.
- Do not rule out a diagnosis of vitamin B12 deficiency based solely on the absence of either anaemia or macrocytosis.
- Consider risk factors for B12 deficiency alongside signs and symptoms when deciding about treatment.
- Studies stating equivalence of oral and IM B12 supplementation are seriously flawed. Most of the evidence base is of very low quality and thus mode of treatment should be decided depending on the cause of deficiency and patient preference.



# KEY MESSAGES

- Patients with Pernicious Anaemia and autoimmune gastritis may also develop coexisting iron, vitamin D, calcium and vitamin C deficiencies due to achlorhydia/ hypochlorydia impairing absorption of these nutrients.
- Consider repeating initial test in patients in whom it was deemed that B12 deficiency was unlikely if patients are still symptomatic after 3-6 months.
- Consider increasing frequency of B12 injections and individualise maintenance treatment based on patient's preference and symptoms.
- Be aware that patients with Pernicious Anaemia / autoimmune gastritis are at higher risk of gastric cancer and should be referred for further investigations should they develop new or worsening GI symptoms.
- Be aware of the signs and symptoms of Subacute Degeneration of Spinal Cord and that this can present in patients who are using nitrous oxide recreationally. Serum B12 levels could be normal or raised. Blood tests including MMA and homocysteine levels should be undertaken and treatment with IM B12 injections initiated immediately and not waiting for the results. Delays in treatment can cause irreversible neurological damage.

# MAIN RESOURCES

1. Vitamin B12 deficiency in over 16s: diagnosis and management NICE guideline [ng239] published: 06 March 2024
2. BMJ Vitamin B12 (practice therapeutics published 20 November 2023)
3. Pernicious Anemia: The hematological presentation of a multifaceted disorder caused by cobalamin deficiency. Published April 2022
4. Guidelines for the diagnosis and treatment of cobalamin and folate disorders – British Journal of Haematology 2014
5. EUR J GEN MED, Volume 12, Issue 3, July 2015, 261-266 – Article on Functional B12 deficiency
6. Oral vitamin B<sub>12</sub> versus intramuscular vitamin B<sub>12</sub> for vitamin B<sub>12</sub> deficiency – Cochrane Review 2018