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GUIDELINES

Vitamin B12 deficiency: NICE guideline summary

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What you need to know

- Offer an initial diagnostic test (total or active B12) for suspected deficiency to people who have at least one common symptom or sign and at least one common risk factor for the condition
- Consider a further test to measure serum methylmalonic acid concentrations in people who have symptoms or signs of vitamin B12 deficiency and an indeterminate total or active B12 test result
- 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 a day

Vitamin B12 deficiency is associated with a range of symptoms and signs, resulting in substantial variation in patient presentation. While epidemiological data are limited, cross sectional studies from the UK and US suggest a prevalence of 3% in people aged 20-39, increasing with age up to about 20% in people aged 85 and over.[1 2] Complications of vitamin B12 deficiency include visual changes, paraesthesia, and ataxia.

In March 2024, the National Institute for Health and Care Excellence (NICE) published new guidance on the diagnosis and management of B12 deficiency.[3] This summary aims to raise awareness of the symptoms and signs, assessment, and management of vitamin B12 deficiency, with particular focus on what is most relevant to general practice and primary care. Readers are directed to the full guideline for a comprehensive review of all recommendations.

Recommendations

NICE recommendations are based on systematic reviews of best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available, recommendations are based on the guideline committee's experience and its opinion of what constitutes good practice. Evidence levels for the recommendations are given in italics in square brackets.

GRADE Working Group grades of evidence

- High certainty—we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate certainty—we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low certainty—our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low certainty—we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

When to test

Vitamin B12 deficiency is a complex condition with significant variability in the type and severity of symptoms that people experience. Following extensive discussion as to which features on presentation and risk factors should be emphasised, the guideline committee prioritised the importance of timely testing while not increasing the volume of testing unnecessarily in people who are unlikely to be deficient. Therefore, the guideline focuses on symptoms and signs commonly attributed to vitamin B12 deficiency where testing is likely to identify people with a clinical deficiency and a diagnosis is most likely to be achieved.

The presence of at least one risk factor and one symptom or sign increases the likelihood of vitamin B12 deficiency. People with symptoms and signs but no risk factors may still have a deficiency, and some people may be unaware of any risk factors they have. Currently, evidence establishing a direct correlation between symptoms, signs, and clinical outcomes is lacking.

- Offer an initial diagnostic test for vitamin B12 deficiency to people who have
  - At least one common symptom or sign (box 1) and
  - At least one common risk factor for the condition (box 2).
- Use clinical judgment when deciding whether to test people who have at least one common symptom or sign (box 1) but no common risk factors (box 2).

  [*Based on the experience and opinion of the guideline committee*]

Box 1: Common symptoms and signs of vitamin B12 deficiency

- Abnormal findings, such as anaemia or macrocytosis, on a blood count
- 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

- Diet low in vitamin B12 (without 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 that exclude 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 syndrome, or type 1 diabetes)
- Medicines:
  - Colchicine
  - H2 receptor antagonists
  - Metformin (see the MHRA safety advice on metformin and reduced vitamin B12[4])
  - Phenobarbital
  - Pregabalin
  - Primidone
  - Proton pump inhibitors
  - Topiramate
- 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

Diagnosis

First line testing

Based on the experience of the guideline committee, active B12 (serum holotranscobalamin) is a more accurate test than total B12 (serum cobalamin) for vitamin B12 deficiency because active B12 measures the biologically active form of vitamin B12 that is available for use by cells. Testing active B12 is more expensive than testing total B12, (active B12 is £18 per test versus total B12 which is £2 per test, mean costs reported by guideline committee members at the time of analysis). This is in part due to active B12 testing mainly being performed by external referral laboratories rather than local hospital laboratories, and increases the turnaround time to receive a result for an active B12test compared with a total B12 test. Despite the suggestion that active B12 is a more accurate test than total B12, evidence is lacking to support a recommendation that would signal a significant and expensive change in practice. Either test is preferrable to not testing when suspicion of deficiency arises from symptoms or signs and risk factors.

This recommendation should not be applied to people who are pregnant or suspected of vitamin B12 deficiency that results from recreational use of nitrous oxide, and guidance on testing for these groups is available in the full guideline.

Further testing

Interpretation and follow-up are dependent on the initial total or active B12 test result. This was based on the experience of the guideline committee and limited, poor quality evidence. The committee recommended considering measuring methylmalonic acid (MMA) as a confirmatory test when initial test results were in an indeterminate range (table 1). Although MMA provides a more reliable diagnosis that reflects the functional status of vitamin B12, it is unsuitable as a first line test. Testing for MMA is expensive (£11-80, range of costs reported by guideline committee members at the time of analysis), requires specialist analytical equipment, and often requires analysis in external laboratories, resulting in an increased time to receive a result.

Table 1 | Interpreting test results for total or active B12

Results if testing total B12 concentrations	Results if testing active B12 concentrations	Likelihood of vitamin B12 deficiency
Less than 180 ng (133 pmol) per litre	Less than 25 pmol per litre	Confirmed vitamin B12 deficiency
180-350 ng (133-258 pmol) per litre	25-70 pmol per litre	Indeterminate test result – possible vitamin B12 deficiency
More than 350 ng (258 pmol) per litre	More than 70 pmol per litre	Test result suggests vitamin B12 deficiency is unlikely

A cost utility analysis was performed to evaluate the cost effectiveness of second line MMA testing if the initial B12 test results were indeterminate. MMA testing before treatment is the most cost effective strategy compared with not testing MMA, with an incremental cost effectiveness ratio of £3946 per quality adjusted life year. Importantly, the model did not account for testing for other underlying causes and assumed that people who had not been diagnosed correctly as B12 deficient on their first visit would attend

primary care once more to gain the correct diagnosis. The model was not able incorporate multiple assumptions stemming from the lack of evidence for the model parameters, including accuracy of MMA testing, prevalence of elevated MMA in the population, variation in quality of life (utility) experienced by people who are B12 deficient, and potential impact on resources because of testing, thereby potentially overestimating savings (owing to uncertainty).

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

  [Based on very low certainty evidence]

Replacement therapy

Management of vitamin B12 deficiency is dependent on the underlying cause. Selection of management options underscored the guideline committee's efforts to balance efficacy, cost effectiveness, and patient preferences in the absence of robust evidence. In this summary, we focus on people with malabsorption conditions specifically. For information and recommendations relating to dietary deficiency, and deficiency caused by medicines or recreational nitrous oxide use, refer to the full guideline.

Malabsorption as the suspected or confirmed cause of vitamin B12 deficiency

All evidence identified for vitamin B12 replacement was in patient populations where the cause of deficiency was unspecified. This was a major limitation in application of the evidence, and was reflected in downgrading of all the evidence because of indirectness. Recommendations were based on seven randomised controlled trials and two observational studies reporting the effect of vitamin B12 replacement on haematological values and experience of the guideline committee.

We identified three economic evaluations that compared oral and parenteral vitamin B12 treatments, all of which assumed equivalent effectiveness between the two modalities.[5-7] Studies ranged in patient selection, setting, and duration of follow-up. Two studies, including a short term cost utility analysis of patients with unexplained fatigue in an Australian primary care setting, concluded that oral treatment was the most cost effective strategy.[5 6] Conversely, one study found that parenteral administration was cheaper unless accounting for the long term savings from avoiding additional GP appointments and blood tests costs.[7] However, none of the studies reflect current treatment costs, and if the models were updated, then parenteral treatment would be the more cost effective option.

In our cost comparison, 50 µg tablets were priced at £0.43 compared with 1 mg tablets at £0.33 at the time of analysis. The guideline committee agreed that it is reasonable to assume that the higher dosage would be at least as effective as the lower strength tablet, and recommended considering the 1 mg tablet as the preferred oral treatment. If people are prescribed a higher dose than 50 µg daily, ie, 100-150 µg daily, then it would be appropriate to use 1 mg, which is the most commonly used dose in current practice. Prescribing a higher dose may be more effective and provide greater health benefit as a larger amount of B12 is being delivered to the bloodstream, and therefore absorbed, while also being convenient to patients by reducing tablet burden.

In the short term, intramuscular treatment is more expensive than oral treatment. For individuals who require long term treatment, such as those with autoimmune gastritis, intramuscular treatment is preferred as it is more cost effective. This recommendation is based on its superior efficacy in the experience of the guideline committee and the economic evidence, as well as the rationale that oral replacement would not be effective if malabsorption were present.

For other malabsorptive states, excluding autoimmune gastritis, where absorption is reduced but not eradicated altogether, some members of the guideline committee suggested that oral replacement may be effective. During the covid-19 pandemic, many people were moved from in-person intramuscular to self-administered oral treatments, but the guideline committee agreed that the evidence to support this as an effective route of administration for this group of patients was inadequate. This view was reiterated by some lay members of the guideline committee, who had experienced a significant worsening of symptoms when switched to oral replacement.

Primary care teams and patients may prefer trialling oral treatment at diagnosis, as prescriptions can be issued directly to people and may be more convenient. No data were identified that support the effectiveness and safety of self-administration of intramuscular replacement.

- 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 a day.

  [Based on moderate to very low certainty evidence]

Implementation

Despite efforts to identify symptoms, signs, and risk factors that may increase the likelihood of diagnosing vitamin B12 deficiency, it is likely that the volume of testing will increase compared with current practice. This may be justified by the prospect of earlier diagnosis and subsequent management of vitamin B12 deficiency, thereby mitigating the risk of unnecessary appointments and investigations, while simultaneously enhancing the quality of life for people with vitamin B12 deficiency.

Not all laboratories offer MMA testing, which is more costly than alternative tests for B12 deficiency, leading to significant cost and resource implications. Increased frequency of MMA testing might be balanced out by fewer primary care appointments, reduced investigations, and reduced onward referrals, leading to earlier and

more appropriate management of B12 deficiency. A local resource impact template is available on the NICE website.[3] Overcoming barriers such as cost and laboratory capacity could involve investment in testing facilities that may potentially reduce the costs of MMA testing in future.

Future research

Developing this guideline was challenging because of a lack of clinical and economic evidence, resulting in many recommendations being based on the expertise of the guideline committee. Nine research recommendations were made, and details can be found in the full guideline. The research recommendations most relevant to the topics covered in this summary are:

- What are the long term outcomes for people with suspected vitamin B12 deficiency when comparing testing of total B12, active B12, serum MMA, or plasma homocysteine?
- What is the clinical and cost effectiveness of vitamin B12 replacement for vitamin B12 deficiency, including the dose, frequency, and route of administration?
- What is the clinical and cost effectiveness of self-administration of vitamin B12 replacement injections for deficiency compared with administration by a healthcare professional?

Guidelines into practice

- What do you ask patients about when deciding whether to test for potential vitamin B12 deficiency?
- How do you determine whether a person with B12 deficiency should be started on oral or intramuscular vitamin B12 replacement?

Further information on the guidance

This guidance was developed in accordance with NICE guideline methodology (www.nice.org.uk/media/default/about/what-we-do/our-programmes/developing-nice-guidelines-the-manual.pdf). A guideline committee was established by NICE, which incorporated healthcare and allied healthcare professionals (two gastroenterologists, two biochemists, two general practitioners, one pharmacist, one haematologist, one dietician, and one care of the elderly physician, in addition to two specialist nurses (one of whom was recruited midway through development), one neurologist, and one psychiatrist/neuro psychiatrist, who were co-opted members) and three lay members. The guideline is available at https://www.nice.org.uk/guidance/ng239. The guideline committee identified relevant review questions and collected and appraised clinical and cost effectiveness evidence. Certainty ratings of the evidence were based on GRADE methodology (www.gradeworkinggroup.org). These relate to the quality of the available evidence for assessed outcomes or themes rather than the quality of the study. The guideline committee agreed recommendations for clinical practice based on the available evidence or, when evidence was not found, based on their experience and opinion using informal consensus methods. The scope and the draft of the guideline went through a rigorous reviewing process, in which stakeholder organisations were invited to comment; the guideline committee took all comments into consideration when producing the final version of the guideline. NICE will conduct regular reviews after publication of the guidance, to determine whether the evidence base has progressed significantly enough to alter the current guideline recommendations and require an update.

How patients were involved in the creation of this article

Maddie Smith is a patient with vitamin B12 deficiency and contributed to the preparation of this manuscript. Guideline committee members involved in this guideline update included lay members who contributed to the formulation of the recommendations summarised here.

The full version of this guideline is available at: https://www.nice.org.uk/guidance/ng239

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The guideline authors' full statements can be viewed at https://www.nice.org.uk/guidance/ng239/documents/register-of-interests-2

Contributorship and the guarantor: Emma Stevenson and Maddie Smith were members of the vitamin B12 deficiency guideline committee and contributed to the development of recommendations in line with NICE processes. Imran Jawaid was the chair of the guideline committee. Toby Sands and Aamer Jawed were technical analysts and provided clinical and economic evidence reports to inform decision making by the guideline committee. The manuscript was drafted initially by Toby Sands and Aamer Jawed. Multiple drafts were reviewed by all authors. Toby Sands is responsible as the guarantor for this manuscript.

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The members of the guideline committee were (shown alphabetically): Ian Beales (gastroenterologist), Medina Brown (lay member), Cassandra Edgar (pharmacist), Mamta Garg (haematologist), Dominic Harrington (biochemist), Imran Jawaid (chair), Rakesh Koria (GP), Louella Oakley (lay member), Harnish Patel (care of the elderly physician), Mark Pritchard (gastroenterologist), Emile Richman (dietician), Willemina Rietsema (GP), Maddie Smith (lay member), Emma Stevenson (biochemist). Co-opted members were: Linda Haste (specialist nurse), Victoria Hetherington (specialist nurse), Nick Kosky (psychiatrist/neuro psychiatrist), Phil Smith (neurologist). More details on guideline committee membership are available at the NICE website.

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