NICE National Institute for Health and Care Excellence

NICE guideline

Vitamin B12 deficiency in over 16s: diagnosis and management

NICE guideline
Published: 6 March 2024

www.nice.org.uk/guidance/ng239

Your responsibility

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Local commissioners and providers of healthcare have a responsibility to enable the guideline to be applied when individual professionals and people using services wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with complying with those duties.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

Overview

This guideline covers recognising, diagnosing and managing vitamin B12 deficiency in people aged 16 and over, including deficiency caused by autoimmune gastritis. It also covers monitoring for gastric cancer in people with autoimmune gastritis.

Who is it for?

- Health and social care professionals providing NHS-commissioned services
- Commissioners of services
- Laboratories
- People with confirmed or suspected vitamin B12 deficiency, their families and carers

Recommendations

People have the right to be involved in discussions and make informed decisions about their care, as described in NICE's information on making decisions about your care.

Making decisions using NICE guidelines explains how we use words to show the strength (or certainty) of our recommendations, and has information about prescribing medicines (including off-label use), professional guidelines, standards and laws (including on consent and mental capacity), and safeguarding.

In this guideline, we do not use the term 'pernicious anaemia' to describe autoimmune gastritis. See the definition of autoimmune gastritis in terms used in this guideline for more details.

1.1 Information and support

1.1.1 When providing information and support to people with suspected or confirmed vitamin B12 deficiency (and their families and carers, if appropriate), follow the recommendations on:

- knowing the patient as an individual, essential requirements of care and enabling patients to actively participate in their care in NICE's guideline on patient experience in adult NHS services
- putting shared decision making into practice in NICE's guideline on shared decision making
- supporting decision making in NICE's guideline on decision making and mental capacity.

1.1.2 Explain to people with suspected vitamin B12 deficiency (and their families and carers, if appropriate) 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.

1.1.3 Explain to people with confirmed vitamin B12 deficiency (and their families and carers, if appropriate) 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
- 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.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on information and support.

Full details of the evidence and the committee's discussion are in evidence review A: information and support.

1.2 Recognising vitamin B12 deficiency

1.2.1 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.

1.2.2 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.

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

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

When to test

1.2.5 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).

1.2.6 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).

See the recommendations on initial tests.

Box 1

Common symptoms and signs of vitamin B12 deficiency

- 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

- 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)
- medicines:
  - colchicine
  - H_2-receptor antagonists
  - metformin (see the MHRA safety advice on metformin and reduced vitamin B12)
  - 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.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on recognising vitamin B12 deficiency.

Full details of the evidence and the committee's discussion are in evidence review B: risk factors and symptoms and signs.

1.3 Diagnosing vitamin B12 deficiency

Initial tests

1.3.1 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.

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

1.3.3 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.

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

1.3.5 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. See the section on factors that can affect total or active B12 test results.

1.3.6 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 (see the section on managing vitamin B12 deficiency).

1.3.7 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 (see recommendation 1.5.7 in the section on managing medicine-induced deficiency).

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on initial tests.

Full details of the evidence and the committee's discussion are in evidence review C: diagnosis.

Factors that can affect total or active B12 test results

1.3.8 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 (including vitamin B12 tablets, injections, or transdermal patches), because this may increase total or active B12 concentrations without fully treating a deficiency
- taking the combined oral contraceptive pill because this can lower total B12 concentrations without causing a deficiency (however, low total B12 concentrations may still mean the person has a deficiency).

For a short explanation of why the committee made this recommendation and how it might affect practice, see the rationale and impact section on factors that can affect total or active B12 test results.

Full details of the evidence and the committee's discussion are in evidence review C: diagnosis.

Thresholds for initial test results

1.3.9 For total or active B12 tests:

- use the thresholds in table 1 to guide diagnosis **or**
- where there is substantial local variation in total B12 validated thresholds, use those set by the laboratory doing the testing.

Table 1

Interpreting total or active B12 test results

Results if testing total B12 concentrations	Results if testing active B12 concentrations	Likelihood of vitamin B12 deficiency
Less than 180 nanograms (133 pmol) per litre	Less than 25 pmol per litre	Confirmed vitamin B12 deficiency

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

1.3.10 Use the laboratory's reference ranges to interpret serum MMA test results when deciding if vitamin B12 deficiency is likely.

1.3.11 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

1.3.12 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 (see table 1). For when to consider starting treatment without waiting for a serum MMA test result, see recommendation 1.3.14.

1.3.13 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.

1.3.14 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)

- 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.

1.3.15 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.

1.3.16 If the person's initial test result suggests vitamin B12 deficiency is unlikely (see the sections on thresholds for initial test results and factors that can affect total or active B12 test results):

- 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.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on thresholds for initial test results.

Full details of the evidence and the committee's discussion are in evidence review C: diagnosis.

1.4 Identifying the cause of vitamin B12 deficiency

1.4.1 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).

1.4.2 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 in line with recommendation 1.5.3 in the section on managing vitamin B12 deficiency where malabsorption is the confirmed or suspected cause, without waiting for the test result.

1.4.3 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.

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

1.4.5 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).

1.4.6 Offer serological testing for coeliac disease where the cause of vitamin B12 deficiency is still unknown after further investigations (see the recommendations on recognising coeliac disease in NICE's guideline on coeliac disease).

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on identifying the cause of vitamin B12 deficiency.

Full details of the evidence and the committee's discussion are in evidence review D: identifying cause.

1.5 Managing vitamin B12 deficiency

1.5.1 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.

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

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on managing vitamin B12 deficiency.

Full details of the evidence and the committee's discussion are in evidence review E: vitamin B12 replacement and self-administration.

Malabsorption as the confirmed or suspected cause of vitamin

B12 deficiency

1.5.3 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.

1.5.4 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.

1.5.5 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.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on managing vitamin B12 deficiency when malabsorption is the confirmed or suspected cause.

Full details of the evidence and the committee's discussion are in evidence review E: vitamin B12 replacement and self-administration.

Medicine-induced vitamin B12 deficiency

1.5.6 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.

1.5.7 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.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on managing medicine-induced vitamin B12 deficiency.

Full details of the evidence and the committee's discussion are in evidence review E: vitamin B12 replacement and self-administration.

Recreational nitrous oxide use as the cause of vitamin B12 deficiency

1.5.8 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.

1.5.9 Advise the person to stop using nitrous oxide recreationally.

1.5.10 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.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on managing vitamin B12 deficiency caused by recreational nitrous oxide use.

Full details of the evidence and the committee's discussion are in evidence review E: vitamin B12 replacement and self-administration.

Dietary vitamin B12 deficiency

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

- ask what they eat or drink, including any foods or drinks that contain vitamin B12
- ask if they are taking, or planning to take, any over-the-counter preparations containing vitamin B12 (when giving advice on over-the-counter oral supplements, see recommendation 1.5.13)
- 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.

1.5.12 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 (see the sections on recognising vitamin B12 deficiency and identifying the cause of vitamin B12 deficiency).

1.5.13 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.

1.5.14 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 (see the NHS webpage on B vitamins) **and**
- consider oral vitamin B12 replacement.

1.5.15 When offering oral vitamin B12 replacement in pregnancy or during breastfeeding, consider a dosage of at least 1 mg a day.

1.5.16 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 multimorbidity or frailty
  - has delirium or cognitive impairment
  - is affected by social issues that may prevent them accessing care, such as homelessness.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on managing dietary vitamin B12 deficiency.

Full details of the evidence and the committee's discussion are in evidence review E: vitamin B12 replacement and self-administration.

Unknown causes of vitamin B12 deficiency

1.5.17 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 (see the section on ongoing care and follow up).

For a short explanation of why the committee made this recommendation and how it might affect practice, see the rationale and impact section on managing vitamin B12 deficiency when the cause is unknown.

Full details of the evidence and the committee's discussion are in evidence review E: vitamin B12 replacement and self-administration.

Self-administration

NICE has made a recommendation for research about self-administration of intramuscular or subcutaneous vitamin B12 replacement.

For a short explanation of why the committee made this recommendation for research, see the rationale section on self-administration of vitamin B12 replacement.

Full details of the evidence and the committee's discussion are in evidence review E: vitamin B12 replacement and self-administration.

1.6 Ongoing care and follow up

1.6.1 Offer an initial follow-up appointment to people who are having vitamin B12 replacement:

- at 3 months after they started treatment, or earlier depending on severity of symptoms, **or**

- at 1 month after they started treatment if they are pregnant or breastfeeding.

1.6.2 At each follow-up appointment, ask the person if their symptoms have improved or worsened, or if they are experiencing new symptoms that could be linked to vitamin B12 deficiency.

Follow-up appointments for people taking oral replacement

1.6.3 If the person is taking oral vitamin B12 replacement, check they are taking the correct dosage (if there are any concerns, follow the recommendations on supporting adherence in NICE's guideline on medicines adherence).

Symptoms have not sufficiently improved, got worse or are new

1.6.4 If the person's symptoms have not sufficiently improved so they are still interfering with their normal daily activities, take into account their treatment preferences and either:

- increase the oral dosage to the maximum licensed dosage **or**
- if they are already taking the maximum licensed dosage for oral treatment, switch to intramuscular vitamin B12 injections.

1.6.5 If the person has new or worsening symptoms, think about an alternative diagnosis and do 1 of the following:

- if the person did not have serum MMA or plasma homocysteine as an initial diagnostic test, consider further testing with:
  - serum MMA, or plasma homocysteine if this test is not available **and**
  - continue with existing treatment while waiting for the test result.
- if the person had serum MMA or plasma homocysteine as an initial diagnostic test, take into account their treatment preferences and either:
  - increase the oral dosage to the maximum licensed dosage **or**

— if they are already taking the maximum licensed dosage for oral treatment, switch to intramuscular vitamin B12 injections.

1.6.6 If a further test to measure either serum MMA or plasma homocysteine suggests a vitamin B12 deficiency, or the result is uncertain, take into account the person's treatment preferences and either:

- increase the oral dosage to the maximum licensed dosage **or**
- if they are already taking the maximum licensed dosage for oral treatment, switch to intramuscular vitamin B12 injections.

1.6.7 Explore alternative diagnoses if the person still has symptoms but a further test to measure serum MMA or plasma homocysteine suggests they no longer have a vitamin B12 deficiency.

Improved or resolved symptoms

1.6.8 Continue with oral vitamin B12 replacement and agree a date for reassessment with the person if:

- their symptoms have resolved or improved so that they are no longer affecting their normal daily activities **and**
- the cause, or suspected cause, of the vitamin B12 deficiency has not been addressed (for example, the person is still taking a medicine that could affect vitamin B12 absorption), **or**
- the cause of deficiency is unknown.

1.6.9 Consider stopping treatment if:

- the person's symptoms have resolved or improved so they are no longer affecting their normal daily activities **and**
- the cause, or suspected cause, of the vitamin B12 deficiency has been addressed (for example, the person has increased their dietary intake of the vitamin).

If stopping treatment, advise the person to come back if symptoms get worse, reappear or they get new symptoms.

Follow-up appointments for people receiving intramuscular replacement

1.6.10 Do not repeat the initial diagnostic test in people who are having intramuscular vitamin B12 replacement.

1.6.11 If the person's symptoms have got worse or have not sufficiently improved so they are still interfering with their normal daily activities, or they have new symptoms of vitamin B12 deficiency:

- increase the frequency of injections if needed, in line with the summary of product characteristics **and**
- think about alternative diagnoses **and**
- agree a date for reassessment of the person's symptoms.

1.6.12 If a person has, or is suspected of having, an irreversible cause of vitamin B12 deficiency:

- continue with lifelong intramuscular injections, even if their symptoms have improved or are no longer present, **and**
- advise them to come back if symptoms get worse, reappear, or they get new symptoms.

1.6.13 If the person's symptoms have improved, or are no longer present, and they have either a reversible cause of vitamin B12 deficiency that has not been addressed, or the cause is unknown:

- continue with intramuscular injections **and**
- agree a date for their next follow up.

1.6.14 If the cause, or suspected cause, of vitamin B12 deficiency has been resolved and the person's symptoms have improved, or are no longer present:

- think about stopping or reducing the frequency of the intramuscular injections **and**
- advise them to come back if their symptoms get worse, reappear, or they get new symptoms.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on ongoing care and follow up.

Full details of the evidence and the committee's discussion are in evidence review F: follow up.

1.7 Monitoring for gastric cancer in people with suspected or confirmed autoimmune gastritis

1.7.1 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.

1.7.2 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.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on monitoring for gastric cancer in people with suspected or confirmed autoimmune gastritis.

Full details of the evidence and the committee's discussion are in evidence review G: monitoring for gastric cancer.

Terms used in this guideline

This section defines terms that have been used in a particular way for this guideline.

Autoimmune gastritis

A chronic inflammatory condition that can lead to vitamin B12 deficiency. Autoimmune gastritis is associated with the presence of auto-antibodies that work against gastric parietal cells and intrinsic factor. These can be detected in the blood but are not always present. Even if they are present, this is not always indicative of autoimmune gastritis.

Autoimmune gastritis is characterised by an inflammation of the body of the stomach, which by itself does not usually cause symptoms but can destroy the parietal cells. In turn, this can reduce the secretion of gastric acid, preventing the release of vitamin B12 from food and impairing iron absorption. Autoimmune gastritis can affect the ability of parietal cells to produce intrinsic factor, which further impairs the absorption of vitamin B12.

Autoimmune gastritis is sometimes referred to as pernicious anaemia. Pernicious anaemia can be a consequence of chronic, severe vitamin B12 deficiency, including deficiency caused by autoimmune gastritis. However, pernicious anaemia in its true sense (that is, life-threatening anaemia) is now extremely rare because of developments in testing and treatment for, and greater awareness of, vitamin B12 deficiency. For this reason, and to prevent any confusion with autoimmune gastritis, we have not used the term 'pernicious anaemia' in the recommendations.

Irreversible cause

A cause of vitamin B12 deficiency that is permanent, even if the deficiency itself can be treated with lifelong vitamin B12 replacement. Examples of irreversible causes include

autoimmune gastritis and some types of gastrointestinal surgery, such as major gastric resection, terminal ileal resection and many bariatric operations.

Over-the-counter preparations

Vitamin B12 supplements (including sublingual vitamin B12 tablets and multivitamin supplements containing the vitamin), injections or transdermal patches that can be obtained without a prescription (for example, in a pharmacy or supermarket, or online).

Reversible cause

A cause of vitamin B12 deficiency that can be reversed, so that the deficiency is resolved, with or without the need for vitamin B12 replacement. Examples of reversible causes include insufficient dietary intake of vitamin B12, and factors that affect absorption such as coeliac disease, some medicines and recreational nitrous oxide use.

Vitamin B12 replacement

Vitamin B12 replacement is where a deficiency is treated with prescribed doses of the vitamin, either as tablets or intramuscular injections, to increase the concentrations in the body.

Recommendations for research

The guideline committee has made the following recommendations for research.

Key recommendations for research

1 Vitamin B12 replacement

What is the clinical and cost effectiveness of vitamin B12 replacement for vitamin B12 deficiency, including the dose, frequency and route of administration?

For a short explanation of why the committee made this recommendation for research, see the rationale section on managing vitamin B12 deficiency.

Full details of the evidence and the committee's discussion are in evidence review E: vitamin B12 replacement and self-administration.

2 Diagnosing vitamin B12 deficiency

What are the long-term outcomes for people with suspected vitamin B12 deficiency when comparing testing of total B12 (serum cobalamin), active B12 (serum holotranscobalamin), serum methylmalonic acid (MMA) or plasma homocysteine?

For a short explanation of why the committee made this recommendation for research, see the rationale section on thresholds for initial test results.

Full details of the evidence and the committee's discussion are in evidence review C: diagnosis.

3 Self-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?

For a short explanation of why the committee made this recommendation for research, see the rationale section on self-administration of vitamin B12 replacement.

Full details of the evidence and the committee's discussion are in evidence review E: vitamin B12 replacement and self-administration.

4 Identifying the cause of vitamin B12 deficiency

What is the clinical and cost effectiveness of pepsinogen, gastrin, parietal cell antibodies and CobaSorb in identifying the cause of vitamin B12 deficiency in people with negative anti-intrinsic factor antibody test results?

For a short explanation of why the committee made this recommendation for research, see the rationale section on identifying the cause of vitamin B12 deficiency.

Full details of the evidence and the committee's discussion are in evidence review D: identifying cause.

5 Follow up

What should be included in a follow-up review for people with vitamin B12 deficiency, including people with autoimmune gastritis?

For a short explanation of why the committee made this recommendation for research, see the rationale section on ongoing care and follow up.

Full details of the evidence and the committee's discussion are in evidence review F: follow up.

Other recommendations for research

6 Risk factors – medicines

Which medicines increase the risk of vitamin B12 deficiency?

For a short explanation of why the committee made this recommendation for research, see the rationale section on recognising vitamin B12 deficiency.

Full details of the evidence and the committee's discussion are in evidence review B: risk factors and signs and symptoms.

7 Risk factors – diet

Which dietary factors increase the risk of vitamin B12 deficiency?

For a short explanation of why the committee made this recommendation for research, see the rationale section on recognising vitamin B12 deficiency.

Full details of the evidence and the committee's discussion are in evidence review B: risk factors and signs and symptoms.

8 Identifying the cause of vitamin B12 deficiency

What is the clinical and cost effectiveness of reflex anti-intrinsic factor antibody testing versus clinician-requested anti-intrinsic factor antibody testing?

For a short explanation of why the committee made this recommendation for research, see the rationale section on identifying the cause of vitamin B12 deficiency.

Full details of the evidence and the committee's discussion are in evidence review D: identifying cause.

9 Monitoring for gastric cancer

What monitoring should be offered to people with autoimmune gastritis to identify gastric cancer?

For a short explanation of why the committee made this recommendation for research, see the rationale section on monitoring for gastric cancer in people with suspected or confirmed autoimmune gastritis.

Full details of the evidence and the committee's discussion are in evidence review G: monitoring for gastric cancer.

Rationale and impact

These sections briefly explain why the committee made the recommendations and how they might affect practice.

Information and support

Recommendations 1.1.1 to 1.1.3

Why the committee made the recommendations

The committee agreed it was important to give people information about vitamin B12 deficiency that is tailored to their individual circumstances, including the condition's various symptoms and causes, and what they can expect from investigations and treatment. They also highlighted difficulties in diagnosing vitamin B12 deficiency because its symptoms vary between individuals and are also linked to many other conditions. Based on their experience and expertise, the committee also agreed that the limitations of diagnostic tests should be explained to people with suspected vitamin B12 deficiency. In addition, they highlighted that some people would need further diagnostic tests, such as those with initial test results that are difficult to interpret because they are indeterminate. Having these discussions would mean people know what to expect from testing and could prevent any distress or concern over unclear test results.

Some causes of vitamin B12 deficiency are irreversible and therefore treatment is needed for life. The committee also wanted to reassure people with an irreversible cause of deficiency that vitamin B12 replacement will not be stopped in the future.

The committee also agreed that people starting treatment should be told that the dosage and form of vitamin B12 replacement could be adjusted or changed if their symptoms do not disappear, get worse or improve.

How the recommendations might affect practice

Information and support are already provided to people with suspected or confirmed vitamin B12 deficiency so these recommendations are unlikely to lead to a resource impact.

Return to recommendations

Recognising vitamin B12 deficiency

Recommendations 1.2.1 to 1.2.6

Why the committee made the recommendations

The committee recognised that vitamin B12 deficiency can be difficult to diagnose based on symptoms or signs alone. This is because symptoms and signs, such as unexplained fatigue, can vary from person to person and can also be indicative of other conditions.

People who have undergone a total gastrectomy or complete terminal ileal resection will need vitamin B12 replacement. This is usually planned for at the time of surgery. However, there is a risk that some people may not continue with, or have problems accessing, treatment (for example, if they lived abroad when they had the surgery). Therefore, the committee highlighted the need to continue or restart treatment in these groups of people.

The committee also made a recommendation to help ensure vitamin B12 deficiency is not missed in people who do not have anaemia or macrocytosis, as there is a common misconception that you cannot have a deficiency unless either, or both, of these signs are present.

They also highlighted an association between mental health problems and vitamin B12 deficiency, but acknowledged that mental health problems are also associated with many other conditions. In light of this, and in the absence of evidence to suggest a strong association between mental health problems and vitamin B12 deficiency, they did not recommend testing based on the presence of mental health problems alone.

When to test

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.

Based on expert witness advice, the committee agreed that the same symptoms and signs would apply in pregnancy and during breastfeeding. They also noted that a poor response to iron treatment is a sign of vitamin B12 deficiency during pregnancy or breastfeeding, so they included this in the list.

The committee highlighted several risk factors for vitamin B12 deficiency to aid diagnosis. Based on expert witness advice, they also agreed all of these would apply during pregnancy and breastfeeding.

Diet was included as a risk factor because anyone who does not take in enough vitamin B12 is at risk of developing deficiency. Based on their experience and expertise, the committee agreed this could include people who follow a diet that excludes, or is low in, animal-source foods. However, they also acknowledged that people who do not eat, or limit their intake of, animal-source foods can still have a balanced diet. These groups can also choose from the wide variety of vegetarian or vegan foods fortified with vitamin B12 that are now available in many shops. The committee also made a recommendation for research into dietary risk factors.

Some conditions, treatments and operations (such as coeliac disease, and pelvic or abdominal radiotherapy) can prevent the body's ability to absorb vitamin B12 properly. The presence of other autoimmune conditions, which often occur together because of an underlying genetic predisposition, increases the risk of vitamin B12 deficiency because these conditions are associated with autoimmune gastritis. Having family members with autoimmune gastritis or another autoimmune condition also increases a person's risk.

Surgery can also cause vitamin B12 deficiency. Evidence suggests that terminal ileal resection is a risk factor. Based on their experience and expertise, the committee also

highlighted other gastrointestinal operations that can increase the risk of vitamin B12 deficiency.

Some medicines have been linked to vitamin B12 deficiency. Evidence suggested that the use of metformin can lead to a decrease in vitamin B12 concentrations. The use of proton pump inhibitors or H_2-receptor antagonists were also found to be risk factors. Based on their expertise, the committee agreed that the use of some medicines for epilepsy, anxiety, nerve pain, or the inflammation and pain caused by gout could also be risk factors. They noted there was a lack of evidence on other medicines that may be linked to vitamin B12 deficiency, so made a recommendation for research on which medicines increase the risk of deficiency.

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. Therefore, they made a recommendation for research in this area.

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.

How the recommendations might affect practice

The symptoms, signs and risk factors included in the recommendations are widely regarded as indications of vitamin B12 deficiency. However, this guideline could lead to a greater awareness of the condition. This may have a resource impact as it could lead to more testing and treatment.

Return to recommendations

Initial tests

Recommendations 1.3.1 to 1.3.7

Why the committee made the recommendations

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 relied on completely to confirm or rule out deficiency.

In the absence of high-quality evidence, the committee agreed that either total B12 (serum cobalamin) or active B12 (serum holotranscobalamin) should be used as the initial diagnostic test for most people. They noted that, while total B12 is the more commonly used test, in their experience active B12 is more accurate. This is because active B12 measures the form of vitamin B12 that can be taken up and used by the body, whereas total B12 measures a combination of both active and inactive forms of the vitamin. However, the active B12 test is also significantly more costly. Recommending it over total B12 would therefore lead to a notable change in practice and would be difficult to justify without evidence of cost effectiveness. The committee did acknowledge that active B12 is a more reliable test during pregnancy, when total B12 concentrations in the body fall even when there is no deficiency, so they recommended active B12 as the initial test for this group based on expert witness advice.

Total and active B12 are not suitable tests for people who use nitrous oxide recreationally because the substance inactivates the vitamin B12 molecule, so the person's total or active concentrations may therefore appear to be normal even when they have a deficiency. The committee acknowledged that in this group of people, both plasma homocysteine and serum methylmalonic acid (MMA) are used as diagnostic tests in current practice. Based on their experience, the committee agreed that plasma homocysteine was more reliable because elevated homocysteine in the body is seen before a rise in MMA. However, they agreed that both tests are likely to be suitable for users of nitrous oxide. The committee also recognised that serum MMA, where available, may be more practical to use in primary care. If plasma homocysteine is used, then the test will need to be done in a secondary care phlebotomy unit because the blood sample needs to be put on ice and promptly transported to the laboratory, which would be challenging in primary care.

People with symptoms or signs of vitamin B12 deficiency linked to severe megaloblastic anaemia and neurological symptoms (especially when related to sub-acute combined degeneration of the spinal cord) need immediate vitamin B12 replacement to prevent worsening outcomes, so the committee recommended this treatment should start without waiting for any test results to come back.

People who are taking a medicine that is known to cause vitamin B12 deficiency may also need to start vitamin B12 replacement while waiting for their test results. This is because, in the committee's experience, the presence of symptoms combined with the use of the medicine suggests the person is highly likely to have a medicine-induced deficiency and they will therefore need vitamin B12 replacement.

The committee emphasised the need to take blood samples from people before they start treatment with vitamin B12 replacement because this could affect their test results. The committee also agreed that people should be asked which over-the-counter preparations containing vitamin B12 they are taking (if any), including different forms like injections or transdermal patches, and at what dosage. This could include some vitamin B12 preparations that are not licensed medicines available to prescribe by healthcare professionals. The committee agreed it was important to have these discussions because over-the-counter preparations can raise vitamin B12 concentrations in the blood and potentially mask a deficiency, depending on how much vitamin B12 they contain.

How the recommendations might affect practice

It is unlikely that these recommendations will lead to a substantial increase in the use of total or active B12 tests because these are already used as initial tests in current practice. If more centres decide to use active B12, there will be an increased cost to the NHS because the test is significantly more expensive. However, this could be offset because, in the committee's view, active B12 is a more accurate test. Overall, it is not anticipated that these recommendations will lead to a significant change in practice.

The recommendation to use plasma homocysteine or serum MMA as the initial test for people who use nitrous oxide recreationally reflects current practice, in most places, and is therefore unlikely to have a big resource impact.

Return to recommendations

Factors that can affect total or active B12 test results

Recommendation 1.3.8

Why the committee made the recommendation

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.

How the recommendation might affect practice

The recommendation reflects current practice and is therefore unlikely to have a big resource impact.

Return to recommendation

Thresholds for initial test results

Recommendations 1.3.9 to 1.3.16

Why the committee made the recommendations

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). For this reason, the committee made a recommendation for research into which diagnostic testing strategies are best for vitamin B12 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. The committee recognised that the cut-offs they specified for test results may increase the risk of false positives. However, these thresholds are likely to be used for people who are already symptomatic and are likely to need treatment, including those with test results near the cut-off for diagnosis. They also noted that treatment is inexpensive, not known to be harmful and could improve the person's health and quality of life.

There are 4 main manufacturers of the total B12 tests. The committee noted that, while 3 out of the 4 have thresholds that are similar to those recommended in the guideline, 1 manufacturer does not. Therefore, the guideline's thresholds should be applicable to most tests, but sometimes a laboratory's own different validated thresholds for total B12 will need to be used instead.

There are no generally accepted reference ranges for serum MMA and plasma homocysteine testing. Therefore, the committee agreed that the laboratory reference ranges would need to be used when interpreting results for these tests. They also highlighted that other factors can affect plasma homocysteine test results and should therefore be taken into account.

There was no evidence to show that using serum MMA to test everyone with an indeterminate result would be clinically and cost effective. It is also an expensive test. However, based on their expertise and experience, the committee acknowledged that a follow-up test with serum MMA could potentially lead to an earlier diagnosis. For this reason, they agreed that this test could be an option for people who had an indeterminate total or active B12 test result and symptoms or signs of deficiency.

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.

The committee identified groups of people who may need treatment if they have an indeterminate test result because a deficiency could adversely affect their health or quality of life. These groups may also need treatment without waiting for a serum MMA

test, if one is being ordered. This was supported by economic analyses which suggested that, in some cases, starting treatment without waiting for a serum MMA test result could be more cost effective than offering treatment afterwards. The committee also agreed that a serum MMA test may still be the best indicator of a deficiency and may be helpful when deciding if the person needs vitamin B12 replacement in the long term. Therefore, the test may still be useful even if treatment is offered.

The committee looked at options for people who have an indeterminate total or active B12 test result but no symptoms or signs. This can happen because of incidental findings, such as the test results of people who do not have a suspected vitamin B12 deficiency but whose vitamin B12 concentrations were tested as part of routine blood investigations (for example, during a preoperative assessment or general health check). The committee agreed this group would not need treatment unless they developed symptoms or signs of vitamin B12 deficiency.

The committee agreed that it was important to investigate other causes of symptoms in people whose initial test results suggested deficiency was unlikely. However, those who still have symptoms 3 to 6 months on may need a repeat of the initial test in case the original result was a false negative.

How the recommendations might affect practice

Adopting the recommended thresholds for total or active B12 may change current practice for some laboratories but is unlikely to have a big resource impact. There are 4 main assays used for assessing total B12 concentrations. Three of the 4 use thresholds for total B12 that closely reflect the recommended thresholds for a diagnosis of vitamin B12 deficiency. If laboratories that use the fourth assay adopt the guideline thresholds instead of the locally validated thresholds, this may lead to a resource impact.

Currently, serum MMA testing is not routinely used in primary care as a follow-up test to aid the diagnosis of vitamin B12 deficiency. The recommendations on further testing will lead to a greater awareness of serum MMA and are likely to increase its use. Not all laboratories currently provide MMA testing and therefore this recommendation is likely to lead to a significant resource impact. However, increased use of serum MMA testing is also likely to lead to faster diagnosis and treatment which, in some cases, could avoid unnecessary investigations or a referral to secondary care.

Return to recommendations

Identifying the cause of vitamin B12 deficiency

Recommendations 1.4.1 to 1.4.6

Why the committee made the recommendations

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. However, the committee agreed it should only be an option for people with suspected autoimmune gastritis because testing everyone believed to have the condition would be very expensive and may not influence treatment (because the person is likely to be receiving vitamin B12 replacement already). They also agreed the test was unnecessary for people who have already had a positive anti-intrinsic factor antibody test (because the result would be the same) or for those who have had a total gastrectomy or complete terminal ileal resection (because the surgery would be the likely cause of deficiency).

Based on expert witness advice and their expertise and experience, the committee recommended anti-intrinsic factor antibody testing for anyone who has suspected autoimmune gastritis and is pregnant or breastfeeding, unless they have previously had a positive test or have undergone certain operations. This is to ensure their health and that of their baby. For this reason, the committee also agreed that intramuscular vitamin B12 replacement should be started without waiting for test results.

The committee agreed that laboratory guidance would need to be followed when interpreting anti-intrinsic factor antibody test results. Based on their expertise and experience, they acknowledged that these test results can often be difficult to interpret, so laboratories would need to provide additional information to aid diagnosis.

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 1 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. They also agreed that more research was needed to determine the most effective investigations for people with negative anti-intrinsic factor antibody tests and so made a recommendation for research on the use of pepsinogen, gastrin, parietal cell antibodies and CobaSorb for identifying the cause of vitamin B12 deficiency.

It was unclear from the evidence whether it is more clinically and cost effective to do reflex testing (laboratories automatically testing) for anti-intrinsic factor antibodies when a low vitamin B12 concentration is detected, or for clinicians to request testing based on their own clinical judgement. Therefore, the committee also made a recommendation for research to compare the use of reflex testing with clinician-requested training.

The committee also highlighted the need to test for coeliac disease when further investigations have not identified a cause of vitamin B12 deficiency. This is in line with NICE's guideline on coeliac disease.

How the recommendations might affect practice

An anti-intrinsic factor antibody test is often requested when autoimmune gastritis is suspected, therefore the recommendations are unlikely to have a big impact. Further investigations are also used in some cases depending on their availability. However, the recommendation may raise awareness of these investigations and potentially lead to an increase in their use, which might require referral to hospital in some cases.

Return to recommendations

Managing vitamin B12 deficiency

Recommendations 1.5.1 and 1.5.2

Why the committee made the recommendations

Evidence on the effectiveness of vitamin B12 replacement was mainly gathered from studies that were based on blood test results and made little reference to quality of life or

other patient-reported outcomes, such as an improvement in symptoms. The aim of treatment is to increase vitamin B12 concentrations. However, based on their experience and expertise, the committee agreed that management of deficiency should also be based on both its cause and factors such as symptoms. They also highlighted a need for further research to identify the optimal treatment strategies for different causes of deficiency, particularly focusing on patient-reported outcomes. Therefore, they made a recommendation for research on the use of vitamin B12 replacement.

Based on their experience and expertise, the committee recommended that all people with vitamin B12 deficiency should be given information on what to expect from treatment and be advised that they may need to seek help if their symptoms are not improving as expected.

Based on expert witness advice, the committee agreed that vitamin B12 replacement should continue if it was started before pregnancy or breastfeeding and its use should be reviewed at a later date. This is because there is no known harm associated with vitamin B12 replacement and stopping treatment may lead to a return of, or worsening, symptoms, potentially leading to harm.

How the recommendations might affect practice

The recommendations reflect current practice and are therefore unlikely to have a big resource impact.

Return to recommendations

Managing vitamin B12 deficiency when malabsorption is the confirmed or suspected cause

Recommendations 1.5.3 to 1.5.5

Why the committee made the recommendations

The committee agreed that anyone with confirmed vitamin B12 deficiency caused by autoimmune gastritis should receive lifelong intramuscular vitamin B12 replacement. This is because their bodies cannot adequately absorb the vitamin through the gastrointestinal tract, often making oral replacement ineffective. Intramuscular injections are also cheaper

than oral replacement if used for 6 months or more, based on the guideline's costing analysis. Autoimmune gastritis is often difficult to diagnose, so the committee agreed that people who are likely to have the condition should have the same treatment as those with a diagnosis. This could prevent the effects of vitamin B12 deficiency becoming permanent.

People who have undergone a total gastrectomy or a complete terminal ileal resection need lifelong intramuscular injections because these types of surgery cause permanent malabsorption.

The committee agreed that people who have malabsorption for other reasons also need vitamin B12 replacement. This includes people who have coeliac disease or have had a partial gastrectomy, partial terminal ileal resection or some forms of bariatric surgery. These groups of people may not need lifelong treatment because, if the malabsorption is managed, the body may be able to absorb vitamin B12. This means the deficiency could potentially be reversed in the long term (for example, in coeliac disease by following a gluten-free diet). Intramuscular treatment was found to be more cost effective than oral replacement when used for 6 months or more. In the committee's experience, injections could be the better option for these groups of people because it can be difficult to judge how much of an oral dose will be absorbed by the body, so injections will help ensure they are getting enough of the vitamin. However, the committee did not rule out the use of oral vitamin B12 replacement, because there was no evidence on its use in these groups of people and therefore there was nothing to suggest it would be ineffective.

Studies comparing oral vitamin B12 replacement with intramuscular injections used an oral dosage of 1 mg a day. The committee agreed that it was important to use the same dosage because there is nothing to suggest a lower dosage is effective in people with suspected or confirmed malabsorption. It is also standard practice to offer intramuscular injections instead of oral treatment when malabsorption is suspected or confirmed.

How the recommendations might affect practice

The recommendations largely reflect current practice and are therefore unlikely to have a big resource impact.

Return to recommendations

Managing medicine-induced vitamin B12 deficiency

Recommendations 1.5.6 and 1.5.7

Why the committee made the recommendations

There was no evidence to suggest that either oral or intramuscular vitamin B12 replacement was better for treating medicine-induced deficiency. So, based on their experience and expertise, the committee agreed that either could be offered depending on clinical judgement and the person's preference. Vitamin B12 replacement should also continue for as long as the person remains on the medicine, because the deficiency is unlikely to be resolved otherwise.

If appropriate, a medicine that can cause vitamin B12 deficiency should be stopped or changed. The committee agreed that if the medicine is stopped or changed and the person no longer has symptoms of vitamin B12 deficiency, the need for vitamin B12 replacement should be reviewed. This is because the cause of deficiency is likely to have been removed.

How the recommendations might affect practice

The recommendations for treating medicine-induced vitamin B12 deficiency reflect current practice and are unlikely to have a resource impact.

Return to recommendations

Managing vitamin B12 deficiency caused by recreational nitrous oxide use

Recommendations 1.5.8 to 1.5.10

Why the committee made the recommendations

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.

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.

How the recommendations might affect practice

The recommendations for managing deficiency caused by recreational nitrous oxide use reflect current practice. They are therefore unlikely to have a resource impact.

Return to recommendations

Managing dietary vitamin B12 deficiency

Recommendations 1.5.11 to 1.5.16

Why the committee made the recommendations

Deficiency caused by diet is potentially reversible. Based on their experience and expertise, the committee agreed it was important to talk to people who have a suspected or confirmed dietary deficiency about what they eat and drink, as well as symptoms, signs and risk factors, to establish if this is the cause of deficiency. They also noted that diet can incorrectly be assumed to be a cause of deficiency in people who get enough of the vitamin through their diet and may have a deficiency for other reasons. This includes people who are vegetarian or vegan who may get vitamin B12 from sources other than meat, fish and dairy products like yeast extract spreads and foods and drinks fortified with vitamin B12, such as some breakfast cereals. Misconceptions about some diets could potentially lead to under-investigation of other causes of deficiency, such as autoimmune gastritis, which can have serious long-term implications if left undiagnosed.

The committee also wanted to raise awareness of the wide variation in forms of oral over-

the-counter supplements containing the vitamin. While some can effectively treat deficiency, others do not contain enough or the right type of the vitamin. This could include pseudo supplements or vitamin B12 analogues which are not appropriate for treating a deficiency. Therefore, the committee agreed to list the types of vitamin B12 people should look out for, should they wish to buy oral supplements.

Based on their experience and expertise, the committee agreed deficiency could be reversed in some people if they changed their diet, without the need for treatment. However, there was a lack of evidence in this area, so they also recommended oral vitamin B12 replacement for some people with a suspected or confirmed dietary deficiency so they get quick and effective treatment if they need it.

Based on expert witness advice, the committee agreed that a dosage of 1 mg may be needed if oral vitamin B12 replacement is prescribed during pregnancy or breastfeeding, when the body can need more vitamin B12. This minimum dosage could help ensure that enough vitamin is being absorbed and protect the health of those taking the treatment, and the health of their baby.

Based on their experience and expertise, the committee agreed that intramuscular vitamin B12 replacement could be the best option for some people. This includes those in whom treatment needs to work quickly because they are at risk of rapid deterioration that could significantly affect their quality of life. Injections could also be a better option if there are concerns about adherence to oral replacement. This could apply to older people who are in or have recently been in hospital, and also have complex comorbidity, or have frailty linked to undernutrition, dementia or decompensation. These groups of people are likely to be prescribed a few different medicines to take on a daily basis, so this would mean they do not have to take an additional medicine. Intramuscular injections may also be more effective in managing the vitamin B12 deficiency. Adherence may also be an issue for some people who are not in hospital but who may find it difficult, or may be unable, to collect, store or regularly take their medicine.

How the recommendations might affect practice

Most of the recommendations for managing dietary deficiency reflect current practice. However, the use of intramuscular instead of oral replacement when there are concerns about adherence will be a change in practice. This is unlikely to have a significant resource impact if no loading doses are needed because intramuscular treatment will always be cost saving compared with oral treatment. If loading doses are needed, then intramuscular

injections will be cost effective if treatment is continued for longer than 6 months.

Return to recommendations

Managing vitamin B12 deficiency when the cause is unknown

Recommendation 1.5.17

Why the committee made the recommendation

In the absence of evidence, the committee used their experience and expertise to recommend vitamin B12 replacement for anyone presenting with a deficiency that does not have a known or suspected cause, and where malabsorption is not suspected. They also agreed that oral vitamin B12 replacement should be considered instead of intramuscular injections, because this group of people should have had any necessary investigations to help rule out malabsorption, and oral treatment should therefore correct the deficiency. However, the committee agreed that oral treatment should be reviewed at the first follow up to make sure it is effective.

How the recommendation might affect practice

The recommendation for managing deficiency of an unknown cause, when malabsorption is not suspected, reflects current practice and is therefore unlikely to impact on resources.

Return to recommendation

Self-administration of vitamin B12 replacement

Recommendation for research 3

Why we made no recommendations

No evidence comparing self-administered intramuscular or subcutaneous vitamin B12 injections with those administered by healthcare professionals was identified. The committee recognised that self-administration could be preferred by some people with

vitamin B12 deficiency and that a precedent was set for it during the COVID-19 pandemic. It also has potential cost savings for the NHS. However, the committee did not recommend self-administration because there was no evidence regarding either the effectiveness or safety of this approach, and the use of subcutaneous vitamin B12 would be off-label. Instead, they made a recommendation for research on self-administration to inform future guidance.

Ongoing care and follow up

Recommendations 1.6.1 to 1.6.14

Why the committee made the recommendations

There was no evidence on the most effective ongoing care and follow-up strategies for people with vitamin B12 deficiency, so the committee made recommendations based on their expertise and experience. For most people who have started treatment, a follow up at 3 months would give enough time to ensure it is working. However, some people with severe symptoms may need an earlier appointment so that treatment can be switched or adjusted if needed. Anyone who is pregnant or breastfeeding should also be followed up sooner to make sure they are getting the treatment they need to protect both their health and that of their baby.

Discussing symptoms at follow up would give an indication of how well treatment is working. The committee agreed that it is important to ask people about changes to their symptoms, especially symptoms that are so severe that they impact on normal daily activities.

The committee also made a recommendation for research into which components of follow-up reviews lead to the best outcomes for people receiving either oral or intramuscular vitamin B12 replacement. In particular, they agreed further research was needed into:

- the measurement of different haematological values
- assessment for dietary intake of vitamin B12
- assessment for the symptoms for vitamin B12 deficiency.

Follow-up appointments for people taking oral replacement

For oral vitamin B12 replacement, the committee agreed it was important to check the person is taking the correct dosage because this can help identify any issues with adherence. Based on their experience and expertise, they also agreed that the need to switch or adjust treatment would depend on how symptoms have changed.

Treatment would need to be reviewed and changed if the person's symptoms have not sufficiently improved. This could be by either increasing the oral dosage up to the licensed maximum or by switching to intramuscular vitamin B12 replacement. The committee agreed the person's preference would need to be taken into account when deciding on any change to treatment.

If the person's symptoms have worsened or they have new symptoms, then it is important to think about alternative diagnoses in case their symptoms are not linked to a deficiency. Further testing with serum MMA or plasma homocysteine could also be options for people who had not had either as a diagnostic test. Based on their experience and expertise, the committee agreed that serum MMA was the better test in these circumstances. However, they were aware that not everywhere has access to this test and that plasma homocysteine could be used instead. The committee also agreed that, if further testing was offered, treatment would need to be continued until the test result is returned to ensure symptoms do not worsen. If further testing suggests a deficiency, or the result is uncertain, then treatment will need to be changed. A test result that suggests deficiency is no longer present while symptoms increase should also prompt exploration of alternative diagnoses.

If symptoms have resolved or improved to the point that they are no longer affecting normal daily activities, then a decision to continue with treatment will depend on the cause of the deficiency and whether it has been addressed. If the cause, or suspected cause, has not been addressed – or the cause is unknown – treatment should continue to prevent symptoms getting worse again. If the cause has been addressed, then treatment could potentially be stopped because symptoms are unlikely to return. However, people should be advised to return if symptoms reappear, because this may indicate that the deficiency has returned and they may need further treatment.

Follow-up appointments for people receiving intramuscular replacement

The committee agreed there was little benefit in repeating the initial diagnostic test in people receiving intramuscular vitamin B12 replacement. This is because the treatment will

influence the test and the result will not be an accurate reflection of how well it is working. Therefore, the committee agreed that it was more important to focus on symptoms and signs at follow-up appointments.

If the person's symptoms have not improved, worsened, or they have new symptoms, then it is likely that the effects of the treatment are wearing off before the next planned injection date. Based on their experience and expertise, the committee agreed that in these circumstances, increasing the frequency of injections may lead to symptom improvement. They also agreed that it is important to think about alternative diagnoses to ensure other causes of the symptoms have not been ruled out and to avoid any unnecessary treatment.

The form of ongoing care and follow up also depends on the cause of the deficiency. The committee agreed that those with an irreversible cause would need to continue with lifelong intramuscular injections. If treatment is working, these groups would not need a regular review. However, people should be advised to return if symptoms reappear, because the dose and frequency of their injections may need to be reassessed.

People with a cause that is potentially reversible would need to continue with treatment until this has been addressed and their symptoms have improved or are no longer present. The same applies to people with an unknown cause of deficiency because until this cause is known and addressed, stopping treatment may cause symptoms to return or get worse. If the cause, or suspected cause, and the symptoms have been addressed, then further treatment is unlikely to be necessary and could be either stopped, or the frequency of the injections could be reduced. However, people should be advised to return if symptoms reappear, because this may indicate the deficiency has returned and they may need further treatment.

How the recommendations might affect practice

The recommendations largely reflect current practice. Usually, people are asked to seek medical help if treatment does not work as well as it should so the recommendations will not have a big resource impact. Offering everyone a follow-up appointment at 3 months or earlier depending on severity of symptoms (or 1 month during pregnancy or breastfeeding) will also help ensure the person has the right diagnosis and treatment. This will help prevent unnecessary treatment, which will outweigh any additional costs related to follow-up appointments.

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Monitoring for gastric cancer in people with suspected or confirmed autoimmune gastritis

Recommendations 1.7.1 and 1.7.2

Why the committee made the recommendations

There was no evidence demonstrating the effectiveness of monitoring people with autoimmune gastritis for gastric cancer. However, based on their experience and expertise, the committee agreed it was important to highlight the increased incidence of gastric adenocarcinoma and gastric neuroendocrine tumours in people with suspected or confirmed autoimmune gastritis. Raising awareness of this may mean people are more likely to report any new or worsening gastrointestinal symptoms to a healthcare professional. They also stressed that people may need referral for gastrointestinal endoscopy if they have new upper gastrointestinal symptoms (for example, dyspepsia, nausea or vomiting) as these could suggest the presence of cancer.

The committee also made a recommendation for research on monitoring for gastric cancer in people with autoimmune gastritis.

How the recommendations might affect practice

These recommendations reflect current practice and are unlikely to have a resource impact.

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Context

Vitamin B12 deficiency is caused by a lack of the vitamin in the diet or problems with absorption from the gastrointestinal tract (for example, because of autoimmune gastritis or major gastric resection). Recreational nitrous oxide use can also cause a deficiency because the substance inactivates vitamin B12 in the body. Vitamin B12 deficiency can lead to a wide range of symptoms and complications, including mental health problems and neurological problems such as cognitive impairment. It is more common in older people and is thought to affect around 5% of people aged between 65 and 74 years and more than 10% of people aged 75 and over.

Vitamin B12 deficiency is usually diagnosed and treated in primary care. A blood test is usually done when people present with symptoms such as unexplained fatigue, which can be common in many conditions, or when there are abnormal findings on other blood tests. Testing is also done when investigating conditions such as anaemia, macrocytosis, and neuropsychiatric or neurodegenerative symptoms or signs.

Treatment for vitamin B12 deficiency depends on the cause but the aim is to replace vitamin B12 and improve the person's symptoms. The most common treatments are oral vitamin B12 replacement, or intramuscular injections given by a healthcare professional.

This guideline aims to improve the diagnosis and management of vitamin B12 deficiency, including deficiency caused by malabsorption (for example, linked to autoimmune gastritis or coeliac disease), the long-term use of some medications and diet. It also aims to reduce complications and improve quality of life for people with suspected and confirmed deficiency.

Finding more information and committee details

To find NICE guidance on related topics, including guidance in development, see the NICE topic page on blood conditions.

For full details of the evidence and the guideline committee's discussions, see the evidence reviews. You can also find information about how the guideline was developed, including details of the committee.

NICE has produced tools and resources to help you put this guideline into practice. For general help and advice on putting our guidelines into practice, see resources to help you put NICE guidance into practice.

ISBN: 978-1-4731-5726-2

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