http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!topicsummary

Anaemia - B12 and folate deficiency

Scenario: Management

Scenario: Management of anaemia - vitamin B12 and folate deficiency

Age from 16 years onwards

[Back to top](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#top)

Assessment

**How should I assess a person with vitamin B12 or folate deficiency anaemia?**

Assessment should include determining the underlying cause of [vitamin B12](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!scenariorecommendation:1) or [folate](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!scenariorecommendation:2) deficiency.

[Back to top](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#top)

**Assessing B12 deficiency**

How should I investigate a person with vitamin B12 deficiency anaemia in primary care?

* Determine whether there is an underlying [cause](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!backgroundsub:2) for the serum vitamin B12 deficiency (for example pernicious anaemia), by checking for serum anti-intrinsic factor antibodies.
  + Note that testing for anti-intrinsic factor antibodies is recommended in people with strong clinical features of B12 deficiency, such as megaloblastic anaemia or subacute combined degeneration of the cord, despite a normal vitamin B12 level. For more information, see the section on [Interpreting results of investigations](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!diagnosisadditional).
  + Checking for gastric anti-parietal cell antibodies is no longer recommended to diagnose pernicious anaemia.
* Determine whether the person has experienced [complications](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!backgroundsub:6) of anaemia, or of vitamin B12 deficiency.

[Back to top](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#top)

Basis for recommendation

The recommendations about checking for an underlying cause for B12 deficiency are based on expert opinion in the British Journal of Haematology *Guidelines for the diagnosis and treatment of cobalamin and folate disorders*[[Devalia et al, 2014](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency" \l "!references/-314396)], and an article on macrocytic anaemias in the ABC of Clinical Haematology [[Hoffbrand and Provan, 2007](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency" \l "!references/-314396)].

**Checking for anti-intrinsic factor antibodies**

* Anti-intrinsic factor antibody is extremely specific for pernicious anaemia, with a high positive predictive value of 95%, but a low sensitivity of 40–60%. This means that about half of people with pernicious anaemia will have anti-intrinsic factor antibody [[Andres et al, 2004](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!references/-314396); [Longmore et al, 2007](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!references/-314396)]. If anti-intrinsic factor antibody is present, pernicious anaemia is very likely, but its absence does not rule out a diagnosis of pernicious anaemia [[Devalia et al, 2014](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency" \l "!references/-314396)].
* The recommendation about checking for anti-intrinsic factor antibodies in people with a normal serum B12 level if there are strong clinical features of B12 deficiency to check for pernicious anaemia is based on expert opinion in *Guidelines for the diagnosis and treatment of cobalamin and folate disorders* published by the British Journal of Haematology [[Devalia et al, 2014](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency" \l "!references/-314396)].

**Not checking for gastric anti-parietal cell antibodies**

* Anti-parietal cell antibody is found in 80% of people with pernicious anaemia, but also in 10% of people without it. However, it has a low specificity of about 50%, which is much lower than that of anti-intrinsic factor antibody [[Andres et al, 2004](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!references/-314396)]. If anti-parietal cell antibody is not present it is unlikely that the person has pernicious anaemia, but its presence is not diagnostic as it can occur in other conditions (for example atrophic gastritis) and older people (16% of normal women over 60 years of age) [[Carmel, 1992](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!references/-314396); [Hoffbrand et al, 2006](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!references/-314396)]. As a result, it is no longer recommended as a diagnostic test for pernicious anaemia [[Devalia et al, 2014](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency" \l "!references/-314396)].

[Back to top](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#top)

**Assessing for folate deficiency**

How should I investigate a person with folate deficiency anaemia in primary care?

* Determine whether there is an underlying [cause](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!backgroundsub:4) for the folate deficiency.
  + If folate levels are low, and the history suggests malabsorption, check for coeliac disease with anti-endomysial or anti-transglutaminase antibodies (depending on the local laboratory).
* Determine whether the person has experienced [complications](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!backgroundsub:6) of anaemia or folate deficiency.

[Back to top](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#top)

Basis for recommendation

This recommendation is based on an article on macrocytic anaemias in the ABC of Clinical Haematology [[Hoffbrand and Provan, 2007](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency" \l "!references/-314396)], a textbook chapter on megaloblastic and other macrocytic anaemias [[Hoffbrand et al, 2006](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency" \l "!references/-314396)], and a patient pathway on anaemia [[NHS Scotland, 2005](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!references/-314396)].

[Back to top](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#top)

Referral

**When should I refer a person with vitamin B12 or folate deficiency anaemia?**

* Seek urgent advice from a haematologist if the person has neurological symptoms, or is pregnant.
* Refer to a haematologist if the cause of vitamin B12 or folate deficiency is uncertain following investigations, or the suspected cause is haematological malignancy (urgently refer) or other blood disorder.
* Refer to a gastroenterologist if:
  + Malabsorption of vitamin B12 (other than due to pernicious anaemia) or folate is suspected.
  + The person has pernicious anaemia and gastrointestinal symptoms, especially if there is a suspicion of gastric cancer (for example co-existing iron deficiency). The urgency of referral will depend on the nature of the symptoms.
  + The person is folate deficient, and antibody testing suggests coeliac disease (positive for anti-endomysial or anti-transglutaminase antibodies).
* Consider referral to a dietician if vitamin B12 or folate deficiency is thought to be due to a poor diet.

[Back to top](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#top)

**Basis for recommendation**

These recommendations are pragmatic advice based on an anaemia patient pathway [[NHS Scotland, 2005](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!references/-314396)], a chapter from the ABC of clinical haematology on macrocytic anaemias [[Hoffbrand and Provan, 2007](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency" \l "!references/-314396)], and guidelines from the National Institute for Health and Clinical Excellence on referral for suspected cancer [[NICE, 2005](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!references/-314396)].

* People with pernicious anaemia have an increased risk of gastric carcinoma or gastric polyps (2–3 times more common than in age- and sex-matched controls) [[Hoffbrand and Provan, 2007](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency" \l "!references/-314396)]. CKS considered this information and expert opinion from reviewers of this CKS topic when making the recommendation about when to refer to a gastroenterologist.
* Further tests which may be considered by specialists if the cause of vitamin B12 deficiency is uncertain include [[Hoffbrand and Provan, 2007](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency" \l "!references/-314396)]:
  + Radioactive vitamin B12 absorption studies.
  + Bone marrow examination (to exclude myelodysplasia, aplastic anaemia, myeloma, or other marrow disorders associated with macrocytosis).
  + Endoscopy and gastric biopsy (vitamin B12 deficiency) or duodenal biopsy (folate deficiency).

[Back to top](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#top)

Treatment for B12 deficiency

**How should I treat a person with vitamin B12 deficiency anaemia?**

* **For people with neurological involvement:**
  + Seek urgent specialist advice from a haematologist.
  + Ideally, management should be guided by a specialist, but if specialist advice is not immediately available, consider the following:
    - Initially administer hydroxocobalamin 1 mg intramuscularly on alternate days until there is no further improvement, then administer hydroxocobalamin 1 mg intramuscularly every 2 months.
* **For people with no neurological involvement:**
  + Initially administer hydroxocobalamin 1 mg intramuscularly on alternate days for 2 weeks.
  + Maintenance dose (where the vitamin B12 deficiency is not thought to be diet related): administer hydroxocobalamin 1 mg intramuscularly every 3 months for life (standard dose). Note that the manufacturers' licence is for every 2–3 months.
  + Maintenance dose (where vitamin B12 deficiency is thought to be diet related): advise people either to take oral cyanocobalamin tablets 50–150 micrograms daily between meals, or have a twice-yearly hydroxocobalamin 1 mg injection. The injection regimen may be preferred in the elderly (who are more likely to have malabsorption), and vegans (as currently available brands of oral cyanocobalamin may not be suitable for vegans).
    - In vegans, this treatment may need to be life-long, whereas in other people with dietary deficiency replacement treatment can be stopped once the vitamin B12 levels have been corrected and the diet has improved.
    - Advise people to eat foods rich in vitamin B12. Foods which have been fortified with vitamin B12 (for example some soy products, and some breakfast cereals and breads) are good alternative sources to meat, eggs, and dairy products.
    - For more information about using vitamin B12 products, see [Prescribing information](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!prescribinginfo).

[Back to top](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#top)

**Basis for recommendation**

* **Vitamin B12 replacement treatment**
  + Vitamin B12 replacement therapy is a well established standard treatment and this recommendation is supported by the British National Formulary [[BNF 64, 2012](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!references/-314396)], Summaries of Product Characteristics (SPCs) [[ABPI Medicines Compendium, 2002](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!references/-314396); [ABPI Medicines Compendium, 2005](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!references/-314396)], a Canadian guideline [[British Columbia Medical Association, 2013](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!references/-314396)], and expert opinion in medical textbooks [[Hoffbrand et al, 2006](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency" \l "!references/-314396); [Hoffbrand and Provan, 2007](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!references/-314396)].
  + Hydroxocobalamin is preferred to cyanocobalamin in the UK. This is because hydroxocobalamin can be given at maintenance dose intervals of up to 3 months, as it is retained in the body for longer [[BNF 64, 2012](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!references/-314396)].
* **Dietary advice**
  + The recommendation on vitamin B12 fortified foods is based on information from the national Expert Group on Minerals and Vitamins [[Expert Group of Vitamins and Minerals Secretariat, 2002](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!references/-314396)], a guidebook (*Nutritional Anaemia*) [[Badham et al, 2007](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency" \l "!references/-314396)], and on expert opinion from medical textbooks [[Hoffbrand et al, 2006](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency" \l "!references/-314396); [Hoffbrand and Provan, 2007](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!references/-314396)].
  + Expert feedback suggests that dietary changes are unlikely to have an effect in the majority of people with pernicious anaemia.

[Back to top](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#top)

Symptoms persist despite maintenance vitaminB12 treatment

**What if a person is still symptomatic despite maintenance vitamin B12 treatment?**

* If a person's symptoms recur before the next injection is due, seek specialist advice from a haematologist.

[Back to top](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#top)

**Basis for recommendation**

* Some experts acknowledge that there is a small group of patients who report a recurrence of their symptoms earlier than 3 monthly.
  + CKS could find no guidelines or evidence on the management of this group.
  + Feedback from expert reviewers differs with regard to whether or not more frequent intramuscular injections of hydroxocobalamin 1 mg are required, and if they are, what regimen to suggest.
  + In the absence of evidence and expert consensus, CKS suggest seeking specialist advice in this situation.

[Back to top](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#top)

Treatment for folate deficiency

**How should I treat a person with folate deficiency anaemia?**

* Give dietary advice: good sources of folate are broccoli, Brussels sprouts, asparagus, peas, chickpeas, and brown rice.
* Prescribe oral folic acid 5 mg daily.
* Check vitamin B12levels in all people before starting folic acid, as treatment can improve well-being such that it can mask underlying B12 deficiency and allow neurological disease to develop.
* In most people, treatment will be required for 4 months. However, folic acid may need to be taken for longer (sometimes for life) if the underlying cause of deficiency is persistent.
* For information on folic acid supplementation in pregnancy, see the CKS topic on [Pre-conception - advice and management](http://cks.nice.org.uk/pre-conception-advice-and-management).

[Back to top](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#top)

**Basis for recommendation**

* The examples of good dietary sources of folate are from the Food Standards Agency [[Food Standards Agency, 2008](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!references/-314396)].
* Folic acid supplementation is a well-established, standard treatment for folate deficiency, and this recommendation is supported by the British National Formulary [[BNF 64, 2012](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!references/-314396)], a Canadian guideline [[British Columbia Medical Association, 2013](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!references/-314396)], and expert opinion in medical textbooks [[Hoffbrand et al, 2006](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency" \l "!references/-314396); [Hoffbrand and Provan, 2007](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!references/-314396)].
* Treatment with folic acid usually results in a rapid improvement in symptoms. In most people, treatment will be needed for only 4 months, as poor diet is the most common cause [[BNF 64, 2012](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!references/-314396)]. Folic acid supplementation for 4 months brings about haematological remission and replenishes body stores.
* Vitamin B12deficiency should be excluded before presuming that a macrocytic anaemia is due to a folate deficiency. If the underlying cause is actually vitamin B12 deficiency but treatment with more than 1 mg folic acid a day is given, this can give the impression that the anaemia has been successfully treated, but vitamin B12 neuropathy will progress and may become irreversible [[Badham et al, 2007](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency" \l "!references/-314396)].
* Concerns have been expressed in recent literature about the potential for harms with long-term supplementation with high folic acid doses [[Powers, 2007](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!references/-314396)]:
  + A possible link has been found with folic acid and an increase in the progression rate of pre-cancerous lesions to cancer (particularly colorectal cancer). However, there is inadequate evidence from human trials to confirm this.

[Back to top](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#top)

Monitoring

**What monitoring of vitamin B12 or folate deficiency treatment is recommended?**

* A full blood count and reticulocyte count should be performed:
  + After approximately 10 days of treatment, to document the response.
    - A rise in the haemoglobin level, and an increase in the reticulocyte count to above the normal range, would be expected as a sign of a positive treatment effect.
    - If the person has vitamin B12 deficiency anaemia and there is no improvement with therapy, check serum folate level (if this has not already been done).
  + After 8 weeks, to confirm a normal blood count.
  + On completion of folic acid treatment, to confirm a response.
* Ongoing monitoring of people being treated with vitamin B12 or folic acid is generally considered unnecessary (unless a lack of compliance with folate treatment is suspected, or anaemia recurs).

[Back to top](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#top)

**Basis for recommendation**

These monitoring recommendations are based on available guidelines [[Hutchinson, 2006](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!references/-314396)], a Best Practice Review [[Smellie et al, 2005](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency" \l "!references/-314396)], an article on the pitfalls of testing for macrocytosis [[Galloway and Hamilton, 2007](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!references/-314396)], the British National Formulary [[BNF 64, 2012](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!references/-314396)], and pharmaceutical manufacturers advice [[ABPI Medicines Compendium, 2012a](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!references/-314396)]. Feedback from expert reviewers was also taken into account.

* The manufacturer states that regular monitoring of the blood is advisable, as hydroxocobalamin should not be given before a megaloblastic marrow has been demonstrated [[ABPI Medicines Compendium, 2012a](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!references/-314396)]. However, expert opinion in a Best Practice review is that people with pernicious anaemia who receive vitamin B12 replacement should not become vitamin B12 deficient, therefore in most cases further monitoring would seem unnecessary, although practices vary and some haematologists would recommend annual full blood counts [[Smellie et al, 2005](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency" \l "!references/-314396)].

**Anaemia - B12 and folate deficiency**

Last revised in July 2015 [Back to top](http://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#top)

**Anaemia - B12 and folate deficiency - Summary**

* Deficiency of vitamin B12 or folate is the most common cause of megaloblastic anaemia.
* Megaloblastic anaemia is characterized by larger than normal developing red blood cells in the bone marrow, with immature nuclei due to defective DNA synthesis. This results in larger than normal red blood cells (macrocytosis).
* Pernicious anaemia (an autoimmune disorder which results in reduced production of intrinsic factor) is the most common cause of vitamin B12 deficiency in the UK. Other causes of vitamin B12 deficiency are rare, but include:
  + Gastric causes (e.g. gastrectomy, gastric resection).
  + Inadequate dietary intake of vitamin B12 (e.g. vegan diet).
  + Intestinal causes (e.g. malabsorption, ileal resection, Crohn's disease).
  + Drugs (e.g. colchicine, neomycin, metformin, anticonvulsants).
* Folate deficiency can occur for a number of reasons, including:
  + Dietary deficiency.
  + Malabsorption.
  + Excessive requirements:
  + Pregnancy, prematurity, and infancy.
  + Malignancy (e.g. leukaemia, carcinoma, lymphoma).
  + Blood disorders (e.g. haemolytic anaemias).
  + Inflammation (e.g. tuberculosis, Crohn's disease).
  + Metabolic causes (e.g. homocystinuria).
  + Excessive urinary excretion (e.g. chronic dialysis).
  + Drugs (e.g. anticonvulsants, colestyramine, sulfasalazine, methotrexate).
* Diagnosis of anaemia caused by vitamin B12 or folate deficiency is made through history, examination, and investigations, including taking a full blood count, blood film, and measuring serum concentrations of vitamin B12 and folate.
  + If vitamin B12 deficiency is found, serum anti-intrinsic factor antibodies should be checked.
  + If there are strong clinical features of B12 deficiency such as megaloblastic anaemia or subacute combined degeneration of the cord, despite a normal serum vitamin B12 level, serum anti-intrinsic factor antibodies should also be checked.
  + If folate levels are low, and the history suggests malabsorption, tests for anti-endomysial or anti-transglutaminase antibodies should be done (depending on the local laboratory) to check for coeliac disease.
* Treatment of B12 deficiency in people with neurologic involvement includes:
  + Seeking urgent specialist advice from a haematologist.
  + Management should ideally be guided by a specialist, but if specialist advice is not immediately available, initially treatment with hydroxocobalamin 1 mg intramuscularly on alternate days until there is no further improvement, then hydroxocobalamin 1 mg intramuscularly every 2 months should be considered — where B12 deficiency is *not* thought to be diet related.
* Treatment of B12 deficiency in people with no neurologic involvement includes:
  + Initial treatment with hydroxocobalamin 1 mg intramuscularly on alternate days for 2 weeks.
  + Maintenance treatment with hydroxocobalamin 1 mg intramuscularly every 3 months for life — where B12 deficiency is *not* thought to be diet related, or
  + Maintenance treatment with oral cyanocobalamin tablets or a twice-yearly hydroxocobalamin 1 mg injection — where vitamin B12 deficiency is thought to be diet related.
* Treatment of folate deficiency includes:
  + Oral folic acid 5 mg daily. In most people, treatment will be required for 4 months. Folic acid may need to be taken longer term (sometimes for life) if the underlying cause of deficiency is persistent.
  + Dietary advice. Good sources of folate are broccoli, brussels sprouts, asparagus, peas, chickpeas, and brown rice.