BMJ Best Practice

Vitamin B12 deficiency

Straight to the point of care

Last updated: Aug 22, 2023

Table of Contents

Overview 3
- Summary 3
- Definition 3

Theory 4
- Epidemiology 4
- Etiology 4
- Pathophysiology 5
- Case history 7

Diagnosis 8
- Approach 8
- History and exam 11
- Risk factors 12
- Tests 14
- Differentials 16
- Criteria 21
- Screening 21

Management 23
- Approach 23
- Treatment algorithm overview 26
- Treatment algorithm 27
- Primary prevention 35
- Secondary prevention 36
- Patient discussions 36

Follow up 37
- Monitoring 37
- Complications 38
- Prognosis 38

Guidelines 40
- Diagnostic guidelines 40
- Treatment guidelines 41

Online resources 42

References 43

Images 55

Disclaimer 57

Summary

Vitamin B12 (cobalamin) deficiency classically presents with megaloblastic anemia, but can also present with neurologic and neuropsychiatric complaints.

Older people, patients with chronic malabsorption, patients with a history of gastric resection or bypass, and those taking certain medications (metformin, proton-pump inhibitors) are at risk.

Early diagnosis is critical in preventing and halting the progression of neurologic disorders such as peripheral neuropathy, subacute combined degeneration of the spinal cord, and dementia.

Methylmalonic acid and homocysteine levels may help to diagnose vitamin B12 deficiency at an early, asymptomatic state.

Cause of vitamin B12 deficiency should be searched for once a diagnosis is confirmed.

Treatment with high-dose oral vitamin B12 therapy may be as effective as intramuscular vitamin B12 therapy.

Definition

Vitamin B12 is an essential vitamin; deficiency generally occurs with inadequate absorption or lack of dietary intake.

Vitamin B12 deficiency is a common condition that can manifest with neurologic, psychiatric, and hematologic disorders. While severe deficiency can cause permanent neurologic damage, earlier manifestations are generally subtle or asymptomatic.

The likelihood of vitamin B12 deficiency can be defined according to the serum vitamin B12 level as follows: <200 picograms/mL indicates probable deficiency; 201 to 350 picograms/mL indicates possible deficiency; and >350 picograms/mL indicates that deficiency is unlikely.[1] [2]

Vitamin B12 level >350 picograms/mL does not exclude vitamin B12 deficiency, particularly if pernicious anemia is suspected. Spuriously normal or high serum vitamin B12 levels have been reported in patients with pernicious anemia due to anti-intrinsic factor antibody (anti-IFAB) interference in laboratory assays.[3] [4] [5] [6]

Epidemiology

The Framingham Offspring Study found up to 39% of US adults at risk for vitamin B12 deficiency (defined as serum vitamin B12 <350 picograms/mL).[10] Prevalence increases with advancing age, and ranges from 5% to 35% in older people depending on the population studied and the methods of diagnosis.[11] [12] [13] [14] [15] [16] [17]

In the US and the UK, the prevalence of vitamin B12 deficiency is approximately 6% in persons younger than 60 years, and nearly 20% in those older than 60 years.[18] Marginal vitamin B12 levels are found in approximately 20% of people in the US and UK.[19] Studies in other world regions including Scandinavia and the Middle East have found evidence of low serum vitamin B12 (<200 picograms/mL) in 25% to 70% of the studied population.[20] [21] [22] [23] [24]

The prevalence of vitamin B12 deficiency is expected to rise with the increasing popularity of veganism and vegetarianism. The exact prevalence of deficiency among vegans and strict vegetarians is difficult to estimate due to study method heterogeneity; however, it may range from as low as 11% to as high as 90% depending on age.[25] [26]

Rising numbers of gastric bypass procedures have led to an increase in vitamin B12 deficiency. Roux-en-Y gastric bypass surgery may cause deficiency in up to half of patients in the initial postoperative years due to inadequate absorption.[27] [28]

Vitamin B12 deficiency may be seen in 20% to 30% of women during pregnancy, and is particularly common if the woman is vegetarian or vegan.[11] [29] One systematic review found that levels of vitamin B12 decrease from the first to the third trimester.[30]

Etiology

Vitamin B12 is an essential vitamin obtained only from diet or by supplementation. Dietary sources include animal and dairy products such as meat, poultry, milk, and eggs. Stores of vitamin B12 in the liver remain in the body for years, so vitamin B12 deficiency depends on chronic, long-term deficiency.

Anything that decreases the intake or the absorption of vitamin B12 places people at risk of vitamin B12 deficiency. In general, etiologies of vitamin B12 deficiency can be categorized into:

- Decreased dietary intake
- Diminished gastric breakdown of vitamin B12 from food
- Malabsorption from the gastrointestinal tract.

Patients at high risk of vitamin B12 deficiency include:

- Vegans and strict vegetarians
- History of gastric or intestinal surgery
- History of atrophic gastritis
- Pernicious anemia, in which autoimmune destruction of the parietal cells (which produce intrinsic factor) leads to reduced vitamin B12 absorption from the gastrointestinal tract
- Gastric malabsorption.

Medications that diminish the breakdown of vitamin B12 from food sources (e.g., H2 receptor antagonists and proton-pump inhibitors) or decrease absorption of vitamin B12 (metformin) can also cause deficiency.[31] [32]

Any malabsorption syndrome can place the patient at risk for vitamin B12 deficiency, such as:

- Crohn disease
- Celiac disease
- Bacterial overgrowth syndromes.

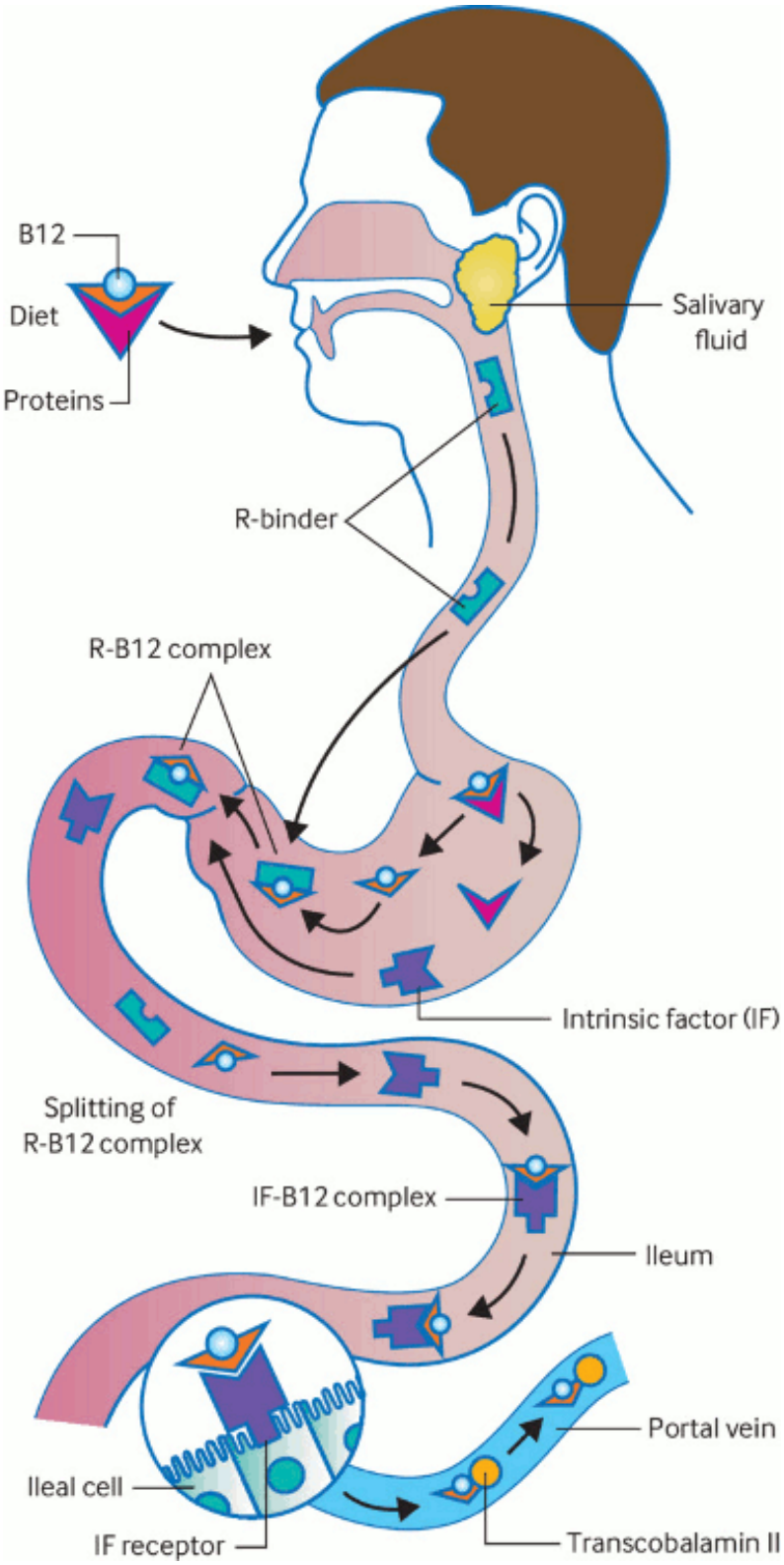
Studies suggest a link between *Helicobacter pylori* infection and vitamin B12 deficiency.[33] [34] However, it is unclear whether the organism, or associated atrophic gastritis, causes vitamin B12 deficiency.[35] There does not appear to be an association between *H pylori* infection and vitamin B12 deficiency in pregnant women.[36]

Anticonvulsant drugs (e.g., carbamazepine) have been associated with vitamin B12 deficiency.[37] [38] The exact mechanism is unclear but might include interference with absorption, plasma binding, cellular metabolism, and renal excretion.

Recreational nitrous oxide (N_2O) misuse, which is increasingly prevalent, has also been linked to vitamin B12 deficiency.[39] In one global systematic review and meta-analysis, up to 85% of reported recreational users were possibly or probably vitamin B12-deficient.[40] N_2O converts the active monovalent form of vitamin B12 to its inactive bivalent form. The neurologic sequelae of N_2O-induced vitamin B12 deficiency can include neuropathy and paralysis.[41]

Pathophysiology

Dietary sources of vitamin B12 (meat, poultry, dairy) are ingested and released from food by peptic acid. Free vitamin B12 then binds to intrinsic factor (IF), which is secreted from the parietal cells of the gastric fundus. The vitamin B12-IF complex travels to the small intestine, where endocytosis occurs in the terminal ileum, by which process it is bound to transcobalamin. The transcobalamin-vitamin B12 complex (holotranscobalamin) is then released into the serum for cell utilization. Any interference in this process can place the patient at risk for vitamin B12 deficiency.



Absorption of vitamin B12. Dietary B12 is released from food in the stomach and binds to R-protein (haptocorrin, this complex is stable in the gastric acidic environment). The R-B12 complex then travels to the duodenum, where B12 binds to intrinsic factor (IF, secreted by gastric parietal cells and therefore lost in pernicious anemia). This B12-IF complex is carried down the small intestine until the terminal ileum, where it attaches to IF receptors and is absorbed into the bloodstream bound to transcobalamin. Over 95% of dietary B12 is absorbed through the IF pathway

Sukumar N et al. Investigating vitamin B12 deficiency. BMJ. 2019 May 10;365:l1865; used with permission

Vitamin B12 is an essential cofactor in DNA synthesis and is closely related to folate metabolism. Specifically, vitamin B12 is an important cofactor in two biochemical processes involving methylmalonic acid and homocysteine as precursors. Deficiency of vitamin B12 impairs the conversion of methylmalonic acid to succinyl co-A. Deficiency of vitamin B12 or folate impairs the conversion of homocysteine to methionine. Methionine is critical in the production of S-adenosylmethionine, which is thought to be important in neural function. Vitamin B12 and folate are thought to be integral in normal hematopoiesis and bone marrow function.

Prolonged and severe deficiency in vitamin B12 can cause neurologic and hematologic disorders, and may manifest with psychiatric symptoms.[42] [43]

Case history

Case history #1

A 68-year-old man presents for a routine physical exam and follow-up for his hypertension, hyperlipidemia, and hypothyroidism. He complains of mild fatigue but is otherwise healthy. Laboratory evaluation is remarkable for a hematocrit of 34, with an MCV of 110 fL. On further query, he denies alcohol use and any other symptoms.

Other presentations

Patients with vitamin B12 deficiency may present with neurologic signs and symptoms (e.g., due to subacute combined degeneration of the spinal cord [caused by upper motor neuron lesions] and/or peripheral neuropathy [caused by lower motor neuron lesions]). Patients may have signs and symptoms of upper and lower motor neuron lesions, such as dysesthesia/paresthesia, ataxia, muscle weakness, and hyperreflexia. Reflexes may be increased, decreased, or absent depending on the location of the lesions.

Clinicians should consider testing for vitamin B12 deficiency in patients complaining of neurologic symptoms, even if vague, as early treatment may prevent permanent neurologic damage. There may be a role for testing for occult deficiency in patients with mild cognitive impairment or dementia, but more research is needed to determine which vitamin B supplements are of benefit for these patients.[7] [8] [9]

Megaloblastic anemia with hypersegmented polymorphonucleated cells is a classic finding in vitamin B12 deficiency, but typically presents in the later stages of deficiency.

Approach

Neurologic disease associated with vitamin B12 deficiency may be irreversible; therefore, early detection is critical in preventing permanent neurologic damage.

Serum vitamin B12 is a standard initial diagnostic test.[1] Low serum vitamin B12 (generally <200 picograms/mL) in the presence of specific clinical symptoms provides evidence of deficiency. Supplementary tests, including markers of tissue deficiency (homocysteine, methylmalonic acid [MMA], and holotranscobalamin), improve earlier diagnosis, and may be considered.

Optimal use of serum vitamin B12 and tissue markers is undefined, but general guidance will help the clinician to determine whether a patient has true vitamin B12 deficiency.

At-risk groups

The clinician should take certain risk factors into account when considering who should be tested for vitamin B12 deficiency.

Advancing age increases risk.[11] [12] [13] [14] [15] [16] Older patients who present with clinical features of deficiency may have vitamin B12 levels within the reference range; further testing may be warranted.[1] [64]

Chronic use of certain medications (specifically metformin, H2 receptor antagonists, proton-pump inhibitors, and anticonvulsants) can also place a patient at risk of deficiency.[31] [32] [37][38] [49] [51] [53]

Recreational nitrous oxide (N_2O) misuse may increase the risk of vitamin B12 deficiency.[39] [40]

Patients with chronic gastrointestinal (GI) illnesses that can cause malabsorption or inadequate absorption, including Crohn disease and celiac disease, and those with a history of upper GI surgery, including gastrectomy, gastric bypass, or ileectomy, should be tested for vitamin B12 deficiency.[27] [45] [46] [47]

Vegans or strict vegetarians who do not take additional dietary supplementation are at risk of developing vitamin B12 deficiency.[26] [48]

Vitamin B12 deficiency may be seen in 20% to 30% of women during pregnancy, and is particularly common if the woman is vegetarian or vegan.[11] [29]

Symptoms and signs

Patients with unexplained neurologic disease (specifically, decreased vibration sense, gait abnormalities, and peripheral neuropathies) should be tested for vitamin B12 deficiency. Neuropsychiatric complaints such as depression and dementia may alert the clinician to an occult vitamin B12 deficiency.[11]

Late signs of vitamin B12 deficiency include angular cheilitis, glossitis of the tongue, and signs of frank anemia and thrombocytopenia.

Initial diagnostic testing

Serum vitamin B12 remains a useful initial diagnostic test due to its widespread availability and familiarity. However, caution must be used when interpreting the values, as there are no well-defined cut-offs for deficiency.[65]

The likelihood of vitamin B12 deficiency can be defined according to the serum vitamin B12 level as follows:[1] [2]

- Probable vitamin B12 deficiency: <200 picograms/mL
- Possible vitamin B12 deficiency: 201 to 350 picograms/mL
- Unlikely vitamin B12 deficiency: >350 picograms/mL.

Vitamin B12 level >350 picograms/mL does not exclude vitamin B12 deficiency, particularly if pernicious anemia is suspected. Spuriously normal or high serum vitamin B12 levels have been reported in patients with pernicious anemia due to anti-intrinsic factor antibody (anti-IFAB) interference in laboratory assays.[3] [4] [5] [6]

A complete blood count with peripheral smear is useful to determine whether there is evidence of macrocytosis and frank anemia, leukopenia, or thrombocytopenia. This suggests a more severe and prolonged vitamin B12 deficiency. However, normal mean corpuscular volume (MCV), hemoglobin, and hematocrit are not useful to rule out vitamin B12 deficiency, as many patients with vitamin B12 deficiency may have normal hematologic parameters.

A peripheral smear may show the classic hypersegmented polymorphonucleated cells and megalocytes found in severe vitamin B12 deficiency with associated macrocytic anemia, but is not sensitive to early vitamin B12 deficiency.

In the era of folic acid fortification, concomitant folate deficiency is rare. In parts of the world where nutritional deficiencies are common, testing for concomitant folic acid deficiency and treatment can help clarify whether true vitamin B12 deficiency coexists.

A reticulocyte count may also be considered to differentiate B12 deficiency from hemolytic anemia. Vitamin B12 deficiency is associated with a low reticulocyte index, whereas hemolytic anemia is associated with a high reticulocyte index.

Clinical assessment of deficiency severity

The severity of the deficiency can be graded clinically as follows:

- Mild to moderate hematologic manifestations: usually asymptomatic with normal hematocrit and an MCV that is at the upper limit of the normal range or mildly elevated.
- Severe neurologic manifestations: subacute combined spinal degeneration, dementia, or cognitive impairment. Subacute combined spinal degeneration is progressive neurologic degeneration of the posterior and lateral columns of the spinal cord; patients present with ataxia, decreased vibration sense, muscle weakness, and hyperreflexia.
- Severe hematological manifestations: pancytopenia and marked symptomatic anemia.

Confirmatory diagnostic testing: serum vitamin B12 <200 picograms/mL

Confirmatory diagnosis is generally unnecessary and empiric treatment should begin. Clinical and serologic response in follow-up confirms vitamin B12 deficiency.[1] [2]

Confirmatory diagnostic testing: serum vitamin B12 201 to 350 picograms/mL

Methylmalonic acid (MMA) can be very sensitive for vitamin B12 deficiency but falsely high levels can occur in renal disease.[1] Additionally, an abnormal MMA level is undefined. Patients with serum vitamin

B12 201 to 350 picograms/mL together with an elevated MMA can be considered to have probable vitamin B12 deficiency. Diagnosis is confirmed if vitamin levels normalize and serum vitamin B12 rises with adequate vitamin B12 treatment.

MMA

Can be elevated (i.e., >0.4 micromol/L) with folate deficiency. Elevated MMA may be spurious and requires subsequent follow-up to determine whether MMA normalizes with adequate treatment. Results should be interpreted with caution in those with renal disease as this can elevate MMA levels.[1]

Homocysteine

Can be elevated (i.e., >15 micromol/L [>2.03 mg/dL]) with folate deficiency, hypothyroidism, and vitamin B12 deficiency.[1] Patients with elevated homocysteine related to vitamin B12 deficiency (when folate deficiency and hypothyroidism are ruled out) should have normalization with empiric vitamin B12 treatment.

Holotranscobalamin (hTC)

This is transcobalamin bound to vitamin B12, and can be a measure of the true functional serum vitamin B12 levels. Several studies have reported greater diagnostic accuracy with the hTC assay than with other assays measuring markers of vitamin B12 deficiency.[66] hTC may be the first marker to be detected with vitamin B12 deficiency. Levels of hTC <35 picograms/L can be consistent with vitamin B12 deficiency.[1] [67] [68] [69]

Confirmatory diagnostic testing: serum vitamin B12 >350 picograms/mL

Patients with pernicious anemia may have spuriously normal or high serum vitamin B12 levels.[3] [4] [5] [6]

If pernicious anemia is suspected in patients with normal or high serum vitamin B12 levels (>350 picograms/mL), further testing for MMA, homocysteine, and hTC should be carried out to determine if vitamin B12 deficiency is present.[1]

Determining the underlying cause of vitamin B12 deficiency

Once the diagnosis of vitamin B12 deficiency is established, an etiology should be sought. While treatment remains the same, vitamin B12 deficiency can lead the astute clinician to discover an underlying malabsorption process such as celiac disease or Crohn disease.

Pernicious anemia can be determined by testing for the following:

- Anti-IFAB: only 50% sensitive, but highly specific for pernicious anemia.[2] Testing for anti-IFAB should be done before initiating vitamin B12 replacement therapy because high vitamin B12 levels may lead to false positive results.[70] [71]
- Antiparietal cell (APC) antibody: highly sensitive (85%), but has low specificity for pernicious anemia because APC antibodies may be elevated in atrophic gastritis.[2]
- Fasting serum gastrin levels rise in gastric achlorhydria and can signify pernicious anemia.[72]

History and exam

Key diagnostic factors

old age (common)

- Older patients have been shown to have increased prevalence of vitamin B12 deficiency.[11] [12] [13] [14] [15] [16]
- This is likely the result of dietary deficiency, decline in gastric function causing malabsorption, and an increased incidence of pernicious anemia.[11]

history of gastric surgery (gastrectomy, or bypass for obesity) (common)

- Patients with gastric bypass or gastrectomy have higher incidence of vitamin B12 deficiency due to malabsorption (from lack of intrinsic factor).[27] [45]
- Routine testing for vitamin B12 deficiency is recommended for all patients following gastric surgery.[74]

Other diagnostic factors

paresthesias (common)

- May be an early and subtle symptom of neurologic damage.[18]

vegan and strict vegetarian diet (uncommon)

- Strict vegetarians and especially vegans are at high risk of vitamin B12 deficiency without multivitamin supplementation.[26] [48]

chronic gastrointestinal disease (e.g., Crohn disease or celiac disease) (uncommon)

- Conditions that cause malabsorption increase the risk of vitamin B12 deficiency.[46] [47]

medication (proton-pump inhibitors, H2 receptor antagonists, metformin, anticonvulsants) (uncommon)

- May be at higher risk by decreasing breakdown of vitamin B12 from food (proton-pump inhibitors and H2 receptor antagonists) or interference with absorption (metformin and anticonvulsants).[31] [32] [37] [38] [49] [50] [51] [52]

ataxia (uncommon)

- Vitamin B12 deficiency can cause posterior column degeneration and eventually lead to ataxic gait.[75]

decreased vibration sense (uncommon)

- Classic sign for posterior column degeneration.

positive Romberg test (uncommon)

- Classic sign for posterior column degeneration.

pallor (uncommon)

- Generally late sign of vitamin B12 deficiency.

petechiae (uncommon)

- Generally late sign of vitamin B12 deficiency.

glossitis (uncommon)

- Generally late sign of vitamin B12 deficiency.[18]

angular cheilitis (uncommon)

- Patients with angular cheilitis should be tested for vitamin B12 deficiency.

cognitive impairment (uncommon)

- In patients with dementia or cognitive impairment, vitamin B12 deficiency should be excluded as a cause.[18] [76]

Risk factors

Strong

age >65 years

- Prevalence increases with advancing age, and ranges from 5% to 35% in older people depending on the population studied and the methods of diagnosis.[11] [12] [13] [14] [15] [16] [17]
- Risk of vitamin B12 deficiency in this population is likely the result of dietary deficiency, decline in gastric function causing malabsorption, and an increased incidence of pernicious anemia.[11]

gastric surgery (bypass or resection)

- In one systematic review, vitamin B12 deficiency was found in 6.5% of patients 12 months after Roux-en-Y gastric bypass surgery compared with only 2.3% of patients prior to surgery.[27] A retrospective study reported deficiency in 12% of patients prior to Roux-en-Y gastric bypass, which increased to 19% in 1 year after surgery and 29% in 3 years.[44]
- Parietal cells of the stomach produce intrinsic factor, which binds to free vitamin B12 and promotes absorption in the terminal ileum. Those who have had gastric surgery or bypass are at high risk of vitamin B12 deficiency due to inadequate absorption.[27] [45]

chronic gastrointestinal (GI) disease

- Chronic GI illnesses (e.g., Crohn disease and celiac disease) can cause malabsorption or inadequate absorption of vitamin B12.
- Vitamin B12 absorption occurs in the terminal ileum; therefore, those with terminal ileum disease are at high risk of vitamin B12 deficiency.[46] In one study, evidence of vitamin B12 deficiency was found in over 50% of patients with Crohn disease who had >20 cm of terminal ileum removed.[47]

vegan or strict vegetarian diet

- The exact prevalence of deficiency among vegans and strict vegetarians (who do not take additional dietary supplementation) is difficult to estimate due to study method heterogeneity; however, it may range from as low as 11% to as high as 90% depending on age.[25] [26]
- One randomized study found that a 4-week vegan diet led to a significant decrease in serum vitamin B12 levels (362 nanograms/dL to 296 nanograms/dL).[48]

metformin use

- Chronic metformin use has been shown to cause low serum vitamin B12 levels and to place patients at risk of vitamin B12 deficiency.[32] [49] [50] [51]
- In one randomized controlled trial of patients with type 2 diabetes, the absolute risk of vitamin B12 deficiency was 7.2% higher in patients treated long-term (4.3 years) with insulin and metformin than in patients receiving insulin and placebo (number needed to harm of 13.8).[52]
- The mechanism is unclear but may be related to malabsorption.

H2 receptor antagonist or proton-pump inhibitor use

- Vitamin B12 bound to food must be freed by peptic acid (secreted from the stomach). Therefore, those who are taking chronic H2 receptor antagonists or proton-pump inhibitors may be at risk for vitamin B12 deficiency.[31]
- One large case-control study found that more than 2 years' use of proton-pump inhibitors or H2 receptor antagonists increased the risk of vitamin B12 deficiency.[53]

Weak

Helicobacter pylori infection

- Studies suggest a link between *H pylori* infection and vitamin B12 deficiency.[33] [34] However, it is unclear whether the organism, or associated atrophic gastritis, causes vitamin B12 deficiency.[35]
- There does not appear to be an association between *H pylori* infection and B12 deficiency in pregnant women.[36]

anticonvulsant use

- Carbamazepine and other anticonvulsants are associated with vitamin B12 deficiency.[37] [38] The exact mechanism is unclear but might include interference with absorption, plasma binding, cellular metabolism, and renal excretion.

nitrous oxide misuse

- Recreational nitrous oxide (N_2O) misuse may increase the risk of vitamin B12 deficiency.[39] [39]
- In one global systematic review and meta-analysis, up to 85% of reported recreational users were possibly or probably vitamin B12-deficient.[40]
- N_2O converts the active monovalent form of vitamin B12 to its inactive bivalent form. The neurologic sequelae of N_2O-induced vitamin B12 deficiency can include neuropathy and paralysis.[41]

diabetes mellitus

- One study reported vitamin B12 deficiency in 22% of people with type 2 diabetes.[54] Vitamin B12 deficiency may be easily overlooked as a cause of neuropathy in people with type 2 diabetes.[54]
- Older patients with diabetes taking metformin may be at greater risk for vitamin B12 deficiency (as metformin can cause vitamin B12 deficiency).[55]

pregnancy

- Vitamin B12 deficiency may be seen in 20% to 30% of women during pregnancy, and is particularly common if the woman is vegetarian or vegan.[11] [29]
- One systematic review found that levels of vitamin B12 decrease from the first to the third trimester.[30]

- Vitamin B12 deficiency in pregnancy may be associated with an increased risk for preterm delivery, lower birth weight, and lower infant levels of vitamin B12.[56] [57]

Tests

1st test to order

Test	Result
CBC • To determine baseline hematocrit, hemoglobin, and MCV. • Useful for diagnosing severe and prolonged vitamin B12 deficiency, but not useful for diagnosing early vitamin B12 deficiency. • Not useful to rule out vitamin B12 deficiency; many patients with documented vitamin B12 deficiency may have normal hematologic parameters.[77]	**elevated MCV, low hematocrit**
peripheral blood smear • Classic hypersegmented polymorphonucleated cells and megalocytes are seen in severe vitamin B12 deficiency, causing megaloblastic anemia. • Megalocytes are red blood cell precursors whose numbers increase due to the importance of vitamin B12 to hematopoiesis. • Can be normal in early deficiency.	**megalocytes, hypersegmented polymorphonucleated cells**
serum vitamin B12 • Serum vitamin B12 <200 picograms/mL indicates probable vitamin B12 deficiency. Confirmatory diagnosis is generally unnecessary and empiric treatment should begin.[1] [2] • Additional testing should be done to rule out possible vitamin B12 deficiency (201-350 picograms/mL). • Patients with serum vitamin B12 >350 picograms/mL are unlikely to have vitamin B12 deficiency. However, vitamin B12 level >350 picograms/mL does not exclude vitamin B12 deficiency, particularly if pernicious anemia is suspected. Spuriously normal or high serum vitamin B12 levels have been reported in patients with pernicious anemia due to anti-intrinsic factor antibody interference in laboratory assays.[3] [4] [5] [6] Further testing for methylmalonic acid, homocysteine, and holotranscobalamin should be carried out to determine if vitamin B12 deficiency is present. • Optimal serum vitamin B12 levels for hematologic and neurologic function are still undetermined.	**<200 picograms/mL (probable deficiency); 201-350 picograms/mL (possible deficiency); >350 picograms/mL (unlikely deficiency, but does not rule out a diagnosis, particularly if pernicious anemia is suspected)**
reticulocyte count • Used to differentiate B12 deficiency from hemolytic anemia. • Low reticulocyte index indicates decreased production, unlike in hemolytic anemia, in which reticulocyte index would be increased.	**low corrected reticulocyte index**

Other tests to consider

Test	Result
methylmalonic acid (MMA) • A marker of vitamin B12 tissue deficiency. • Caution in renal disease, as elevated MMA levels occur.[1] • Elevated MMA may be spurious and requires subsequent follow-up to determine whether MMA normalizes with adequate treatment.	**elevated (>0.4 micromol/L, but may be lab-specific)**
homocysteine • A marker of vitamin B12 tissue deficiency. • Not as specific as methylmalonic acid (MMA) for vitamin B12 deficiency.[1] Also elevated in folate deficiency and hypothyroidism.	**elevated (>15 micromol/L [>2.03 mg/dL], but may be lab-specific)**
holotranscobalamin (hTC) • A marker of vitamin B12 tissue deficiency. • Measures vitamin B12 bound to transcobalamin. Low levels along with low normal serum vitamin B12 suggest inadequate absorption. • Several studies have reported greater diagnostic accuracy with the hTC assay than with other assays measuring markers of vitamin B12 deficiency.[66]	**<35 picograms/L is diagnostic**
anti-intrinsic factor antibody (anti-IFAB) • Once vitamin B12 deficiency is confirmed, testing for anti-IFAB can determine whether pernicious anemia is the cause. Only 50% sensitive, but highly specific for pernicious anemia.[2] • Testing for anti-IFAB should be done before initiating vitamin B12 replacement therapy because high vitamin B12 levels may lead to false positive results.[70] [71]	**positive if pernicious anemia is the cause**
antiparietal cell (APC) antibody • Once vitamin B12 deficiency is confirmed, APC antibody can, in conjunction with other tests, help to determine whether pernicious anemia (PA) is the cause. • Highly sensitive (85%), but has low specificity for PA because APC antibodies may be elevated in atrophic gastritis.[2]	**positive result may suggest PA; positive result is not sufficient for diagnosis of PA because APC antibodies may be elevated in atrophic gastritis**
serum gastrin (fasting) • Gastrin levels rise in gastric achlorhydria and can signify pernicious anemia.[72]	**elevated if pernicious anemia is the cause**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Folic acid (vitamin B9) deficiency	• Generally does not present with neurologic symptoms. Rare in the present era of folic acid fortification in the US.	• Serum folate levels are low. • Be aware that low serum folate can result in falsely low vitamin B12 levels. • Treat with folic acid and retest.
Myelodysplastic syndrome (MDS)	• Presents with macrocytic anemia and is difficult to differentiate from vitamin B12 deficiency initially. • MDS is a group of disorders characterized by a clonal chromosomal abnormality, ineffective and dysplastic hematopoiesis resulting in ≥1 cytopenias, and a varying predilection to develop acute myeloid leukemia. • These disorders can arise primarily without any precipitating event or may be related to previous treatment with either chemotherapy or radiation.	• CBC in MDS shows normochromic or macrocytic red cells; about 40% of patients have neutropenia, and >30% have thrombocytopenia. Morphologic abnormalities include oval macrocytic red cells and granulocytes with the pseudo-Pelger-Huet anomaly (hypogranular and hypolobulated granulocytes). • Bone marrow histopathology in MDS demonstrates dysplasia in a proportion of undifferentiated myeloblasts. • Prussian blue iron staining of bone marrow aspirate can show ringed sideroblasts (abnormal erythroid precursor cells that have granules around the nucleus).
Alcoholic liver disease	• May present with macrocytic anemia and nutritional deficiencies. History should reveal alcohol use.	• Elevated liver enzymes. • Liver biopsy histopathology shows fatty change, inflammation, and variable amounts of fibrosis leading to cirrhosis in severe, chronic alcoholic liver disease.
Hypothyroidism	• May present with macrocytic anemia. • May show signs of muscle and joint pain, weakness in the extremities, and fatigue; delayed relaxation of deep tendon reflexes strongly suggests hypothyroidism.	• Elevated thyroid-stimulating hormone, decreased T3 and T4, and elevated creatine kinase.
Peripheral neuropathy	• Compression neuropathies, and neuropathies due to diabetes or thyroid disease, may be difficult to	• Nerve conduction studies and electromyogram are helpful in confirming and characterizing neuropathy;

Condition	Differentiating signs / symptoms	Differentiating tests
	differentiate from neurologic symptoms of vitamin B12 deficiency.	that is, demyelinating, axonal, polyneuropathy, mononeuropathy multiplex, radiculopathy, or plexopathy. • Treatment with vitamin B12 may improve symptoms, but neuropathy may be irreversible.
Diabetic neuropathy	• Paresthesia is a common feature and may occur in the extremities as a result of neuropathy in those with prolonged undiagnosed diabetes. Other types of neuropathy may be present in diabetes, including autonomic neuropathy.	• Elevated fasting glucose or HbA1c. • Antiglutamic acid decarboxylase antibodies, islet cell antibodies, and insulin autoantibodies are present in 85% of patients with type 1 diabetes at the time of diagnosis, but may disappear within a few years.
Drug-induced macrocytosis	• Macrocytosis due to certain medications, including hydroxyurea, methotrexate, zidovudine, azathioprine, capecitabine, and cladribine.	• Usually a clinical diagnosis. Serum drug levels may confirm the association.
Dementia	• Characterized by cognitive (memory) changes, psychiatric symptoms, personality changes, problem behaviors, and changes in day-to-day functioning. • May be due to multiple different factors that are clinically indistinguishable from vitamin B12 deficiency.	• A mental state exam or neuropsychiatric testing should be conducted if the diagnosis is uncertain. • Vitamin B12 testing is normal.
Depression	• Characterized by persistent low mood causing varying levels of social, cognitive, occupational, and physical dysfunction.[78]	• Vitamin B12 testing is normal.
Pernicious anemia (PA)	• Patients present with symptoms of anemia and vitamin B12 deficiency. They may also have fever and complain of gastric pain or discomfort. Common features include tiredness, dyspnea, paresthesias, sore red tongue, diarrhea, and mild jaundice.	• Once vitamin B12 deficiency is confirmed, testing for anti-intrinsic factor antibody (anti-IFAB) can determine whether PA is the cause. It is only 50% sensitive, but highly specific for PA.[2] Testing for anti-IFAB should be done before initiating vitamin B12 replacement therapy because high vitamin B12

Condition	Differentiating signs / symptoms	Differentiating tests
		• levels may lead to false positive results.[70] [71] • Antiparietal cell (APC) antibody can, in conjunction with other tests, help to determine whether PA is the cause. It is highly sensitive (85%), but has low specificity for PA. APC antibodies may be elevated in atrophic gastritis.[2] • Once a patient is given intrinsic factor and vitamin B12 level is normal, gastrin levels will normalize.
Crohn disease	• Crohn disease can affect any part of the gastrointestinal tract, and symptoms may be extremely variable. • Increased risk for B12 deficiency occurs with ileectomy >20 cm.[47]	• The classic findings on histologic exam include involvement of all layers of the bowel wall by granulomas, ulcerations, and acute and chronic inflammation.
Celiac disease	• Patients present with unexplained gastrointestinal symptoms, chronic diarrhea, unexplained iron deficiency anemia, vitamin D deficiency, or a skin rash consistent with dermatitis herpetiformis. • Other situations include failure to thrive, short stature, recurrent severe aphthous stomatitis, recurrent spontaneous abortion, and infertility.	• Immunoglobulin A antigliadin and antiendomysial antibodies. • Small-bowel histology is the most specific and sensitive test, showing villous atrophy and mucosal inflammation with hyperplastic changes to crypts. • Iron deficiency anemia is the most common clinical presentation in adults. • Folate (and less commonly vitamin B12) deficiency may lead to macrocytic anemia.
Peptic ulcer disease from Helicobacter pylori infection	• *H pylori* is a gram-negative, microaerophile bacterium that inhabits the stomach and duodenum. It causes a chronic low-level atrophic gastritis and is strongly linked to the development of duodenal and gastric ulcers and stomach cancer. • Over 80% of people infected with the bacterium are asymptomatic.	• The carbon urea breath test is positive. • The most reliable method for detecting *H pylori* infection is endoscopic biopsy. Histopathology shows gastric atrophy, inflammation, and bacterial organisms on special stains.
Chronic pancreatitis	• History of gallstone disease or alcohol misuse.	• Ultrasound or CT imaging of the abdomen may reveal

Condition	Differentiating signs / symptoms	Differentiating tests
	• Characterized by recurrent or persistent abdominal pain and progressive injury to the pancreas and surrounding structures, resulting in scarring and loss of function.	fibrosis and calcification of the pancreas. • Evaluation of pancreatic enzymes is the most sensitive and specific test for diagnosing mild to moderate pancreatic insufficiency or chronic pancreatitis, but it is available in only a few centers. Pancreatic juice is collected with a gastroduodenal tube during exogenous hormone stimulation with cholecystokinin and/or secretin. • Helps differentiate pancreatic from nonpancreatic types of malabsorption.
Small-intestinal bacterial overgrowth	• History may show conditions that alter intestinal anatomy, motility, and gastric acid secretion. These include use of proton-pump inhibitors and anatomic disturbances in the bowel, including fistulae, diverticula, and blind loops created after surgery.	• The definitive investigation requires culture of jejunal fluid that grows >10^5 bacteria/mL. • Hydrogen breath testing may show malabsorption but is not very sensitive or specific for bacterial overgrowth. • A trial of treatment with antibiotics for 1 week may give the diagnosis.
Zollinger-Ellison syndrome	• A condition caused by a gastrin-secreting tumor that causes hypersecretion of gastric acid leading to ulcer disease. It most commonly presents with abdominal pain, diarrhea, and gastroesophageal reflux. Less common presentations include weight loss, gastrointestinal bleeding, nausea, and vomiting.	• Elevated level of fasting serum gastrin in the absence of achlorhydria, and either a positive secretion test or histologically demonstrated neuroendocrine tumor.
Tropical sprue	• Believed to be initiated or sustained by an undefined infection. • Presents with symptoms and signs of malabsorption, stomach pain, diarrhea, and bloating. • The relapse rate is substantial in treated patients who remain in, or	• Endoscopy and small bowel biopsy reveals progressive villus atrophy in the small intestine similar to celiac disease. • Therapeutic trial with tetracyclines for 6 months normalizes mucosal structure in the small intestine.

Condition	Differentiating signs / symptoms	Differentiating tests
	return to, endemic areas in the tropics.	
Fish tapeworm (Diphyllobothrium latum)	• Fish tapeworm is native to Scandinavia, western Russia, and the Baltic states. Now present in North America, especially the Pacific Northwest. • Infection arises following eating raw fish or fish products. • Patients present with symptoms of malnutrition including anemia.	• Fish tapeworm eggs appear in the feces 5 to 6 weeks after infection, and fecal exam may confirm the diagnosis.
HIV infection	• Malnutrition is common in HIV disease, particularly in resource-poor areas. A cycle of opportunistic infection causing loss of weight and poor appetite, together with diarrhea and malabsorption, contributes to malnutrition.	• Enzyme-linked immunosorbent assay (ELISA) testing should be ordered when HIV testing is indicated. False-negatives may occur during window period immediately after infection and before antibodies to HIV have developed. A positive result should be confirmed with a Western blot or second ELISA. The window period can be reduced to 2-4 weeks by using fourth-generation tests that detect IgM and IgG antibodies to HIV and p24 antigen.[79] [CDC: HIV - laboratory tests] (https://www.cdc.gov/hiv/testing/laboratorytests.html)
Alpha-thalassemia	• An inherited autosomal recessive blood disease. • Vitamin B12 requirement is increased in alpha-thalassemia; vitamin B12 deficiency may be the presenting feature. Patients present with anemia, hepatosplenomegaly, leg ulcers, and bone pain. This disease is more common in Mediterranean countries, Asia, the Middle East, and South America.	• CBC and peripheral smear show microcytosis, erythrocytosis, hypochromia, and mild anemia. • A diagnosis can be made by a combination of family studies and the ruling out of both iron deficiency anemia and beta-thalassemia trait. • A definitive diagnosis can be made by DNA sequencing of the alpha-globin chain.
Multiple sclerosis	• Neurologic manifestations of vitamin B12 deficiency can mimic clinical symptoms of	• Brain MRI typically shows areas of demyelination.

Condition	Differentiating signs / symptoms	Differentiating tests
	multiple sclerosis. However, in almost all cases of multiple sclerosis there are also brain lesions. • Variable presentation: multiple episodes separated by space (i.e., neurologic symptoms result from lesions in different central nervous system sites) and time. Symptoms include progressive limb weakness, gait difficulty, ataxia, loss of balance, and paroxysmal vertigo.	• Cerebrospinal fluid (CSF) exam shows elevated IgG and oligoclonal banding.
Syphilis (tabes dorsalis)	• History of syphilis infection or sexually transmitted infection. • Neurologic symptoms of tabes dorsalis and subacute combined spinal degeneration may be similar.	• The Venereal Disease Research Laboratory (VDRL) reaction test alone cannot always be depended on in differential diagnosis. • CSF exam is required to diagnose neurosyphilis. • CSF VDRL reactivity test is specific but not sensitive for neurosyphilis. • CSF fluorescent treponemal antibody absorption reactivity test is sensitive but not specific for neurosyphilis.

Criteria

Serum vitamin B12 levels

The likelihood of vitamin B12 deficiency can be defined according to the serum vitamin B12 level as follows:[1] [2]

- Probable vitamin B12 deficiency: <200 picograms/mL
- Possible vitamin B12 deficiency: 201 to 350 picograms/mL
- Unlikely vitamin B12 deficiency: >350 picograms/mL.

Vitamin B12 level >350 picograms/mL does not exclude vitamin B12 deficiency, particularly if pernicious anemia is suspected. Spuriously normal or high serum vitamin B12 levels have been reported in patients with pernicious anemia due to anti-intrinsic factor antibody (anti-IFAB) interference in laboratory assays.[3] [4] [5] [6]

Screening

Screening is controversial, but clinicians should take certain risk factors into account when considering testing for vitamin B12 deficiency.

- Advancing age: increased risk for vitamin B12 deficiency.[11] [12] [13] [14] [15] [16]
- Chronic use of certain medications: metformin, proton-pump inhibitors, and anticonvulsants can place a patient at risk of deficiency.[31] [32] [37] [38] [49] [50] [51] [52]
- Malnutrition and vegan or strict vegetarian diet: increased risk of vitamin deficiency, and serum vitamin level monitoring may be offered.[26] [48]
- Chronic gastrointestinal illness: can cause malabsorption or inadequate absorption (e.g., Crohn disease, celiac disease).[46] [47]
- Gastric surgery (bypass or resection): high risk of vitamin B12 deficiency due to inadequate absorption.[27] [45] Patients who have undergone gastric surgery or terminal ileectomy should be screened regularly for deficiency.[27] [45] [46] [47] [74]
- Diabetic polyneuropathy (DPN), or worsening DPN: may be at increased risk for concomitant vitamin B12 deficiency.[80]
- Peripheral neuropathy (idiopathic): patients may be at increased risk for concomitant vitamin B12 deficiency.[7]

A two to threefold excess risk of gastric cancer has been noted in patients with pernicious anemia, and endoscopic follow-up may be required in these patients.[81]

Approach

Patients with severe hematologic or neurologic symptoms of vitamin B12 deficiency require immediate treatment with an intensive regimen of cyanocobalamin or hydroxocobalamin over 1 month, followed by ongoing maintenance doses.

Patients with mild to moderate symptoms of vitamin B12 deficiency should be started and continue on maintenance-level doses of cyanocobalamin or hydroxocobalamin.

Asymptomatic patients with a high risk of vitamin B12 deficiency (e.g., vegans and strict vegetarians, older patients, those with chronic gastrointestinal [GI] illnesses) require maintenance-level doses of cyanocobalamin or hydroxocobalamin (because hematologic and neurologic complications may be irreversible once they develop).

If the cause of the vitamin B12 deficiency is not yet established, or if vitamin B12 deficiency is clinically suspected despite normal or high serum vitamin B12 levels, treatment should be commenced while awaiting results of further investigations (e.g., anti-intrinsic factor antibody testing).

Vitamin B12 therapy options

Options available include parenteral (intramuscular or subcutaneous), oral, sublingual, or intranasal cyanocobalamin.

Parenteral cyanocobalamin or hydroxocobalamin

By far the most reliable and most familiar treatment for vitamin B12 deficiency, particularly for patients with severe anemia and/or neurologic disease (subacute combined spinal degeneration, dementia, or cognitive impairment).[42] In Europe, parenteral hydroxocobalamin is more commonly used than parenteral cyanocobalamin. Hydroxocobalamin is retained longer in the body than cyanocobalamin, but superiority to cyanocobalamin has not been established in clinical trials.

Oral cyanocobalamin

Preferred to intramuscular administration.[82] High-dose oral cyanocobalamin can be adequately absorbed, even in patients with pernicious anemia or significant terminal ileum resection.[83] [84] [85] Absorption can be maximized by administering on an empty stomach. Findings from one Cochrane review suggest that oral cyanocobalamin is at least as effective as intramuscular cyanocobalamin in patients with vitamin B12 deficiency.[86]

Sublingual and intranasal cyanocobalamin

Although effective, sublingual and intranasal cyanocobalamin are generally not used in the treatment of vitamin B12 deficiency due to limited evidence and limited knowledge regarding optimal dosing.[87] [88] [89] Intranasal cyanocobalamin may be considered in patients who have undergone bariatric surgery.[74]

Patients presenting with severe symptoms

Patients presenting with severe hematologic (pancytopenia and marked symptomatic anemia) or neurologic (subacute combined spinal degeneration, dementia, or cognitive impairment) symptoms of vitamin B12 deficiency require acute and urgent treatment.[90]

Patients with symptomatic anemia and pancytopenia require hospital admission and hematologic specialist referral, and, rarely, may require red blood cell (RBC) transfusion. If there are signs of congestive cardiac failure, packed RBCs should be given together with low-dose diuretic therapy. An acute regimen of parenteral cyanocobalamin is given until significant reticulocytosis is seen in the marrow.[91] Folic acid supplementation may help reverse the hematologic abnormalities.

Replacement therapy may potentially improve cognition outcomes in patients with noted cognitive impairment and vitamin B12 deficiency.[92]

Patients with severe neurologic symptoms may require neurologic and psychogeriatric referral and evaluation while commencing the acute parenteral treatment regimen. In some cases, neurologic symptoms may be irreversible despite normalization of serum vitamin B12 levels.

Ongoing maintenance treatment is with once-daily oral cyanocobalamin, or once-monthly parenteral cyanocobalamin.

Patients with mild to moderate symptoms

Acute and maintenance treatment of patients with mild to moderate symptoms of vitamin B12 deficiency (e.g., mild anemia, dysesthesia/paresthesias, polyneuropathy, depression) is with once-daily oral cyanocobalamin or once-monthly parenteral cyanocobalamin, depending on clinician preference. Patients treated with oral cyanocobalamin should respond within 8 weeks. If serum vitamin B12 does not rise significantly after this time, clinicians should switch to parenteral cyanocobalamin (if not already used) or consider other causes.

Asymptomatic or borderline deficiency in high-risk patients

High-risk patients (e.g., older patients, and those with restrictive diets or chronic GI illness) should be monitored for vitamin B12 deficiency. Treatment with oral or parenteral cyanocobalamin should be considered, even if they are asymptomatic. This is because the hematologic and neurologic complications of vitamin B12 deficiency may be irreversible once they develop.

Older patients (>65 years)

Dietary advice should be given on the importance of eating animal-derived foods (such as meat, fish, eggs, and milk), and taking multivitamin supplements. Older people who have a poor diet should be counseled that lifelong monitoring and supplements may be required.

Vegan or strict vegetarian diet

Should be counseled to supplement their diet with appropriate vitamin B12-fortified foods and multivitamin supplements in order to meet the recommended dietary allowance of 2.4 micrograms/day.[58] [93]

Chronic GI illness

Patients with a chronic GI illness that can cause malabsorption or inadequate absorption (e.g., pernicious anemia, Crohn disease, celiac disease) or who have undergone gastric surgery or terminal ileectomy should be treated with parenteral cyanocobalamin.[1] [94]

Bariatric surgery

Patients who have had bariatric surgery may not be able to adequately maintain serum vitamin B12 levels with multivitamins; therefore, oral, parenteral, or intranasal cyanocobalamin should be given.[74] [95] An oral multivitamin supplement optimized for bariatric surgery has shown potential benefit in reducing vitamin deficiencies following Roux-en-Y gastric bypass surgery, but the evidence is limited.[96]

Pregnancy and breast-feeding

Up to 20% to 30% of pregnant women may be at risk for vitamin B12 deficiency.[11] Deficiency found in pregnancy should be treated, even if the woman is asymptomatic, because deficiency may be associated with adverse risk for preterm delivery and lower birth weight.[11] [29][57] Treatment of pregnant women is generally the same as for nonpregnant patients.

Pregnant and breast-feeding women who have a strict vegetarian or vegan diet should be counseled about adequate intake of vitamin B12 and supplementation.[29] Breast-feeding women who adhere to a vegan diet will only provide adequate vitamin B12 for their infant if the mother satisfies vitamin B12 requirements through supplementation.[97]

Monitoring response to treatment

Brisk reticulocytosis in the bone marrow occurs within 1-2 weeks of initiating treatment in patients with severe anemia due to vitamin B12 deficiency.

Other markers of deficiency, including methylmalonic acid, homocysteine, and mean corpuscular volume, should normalize in 8 weeks with adequate treatment. Serum vitamin B12 (serum cobalamin) levels should return to normal before starting maintenance therapy.

Maintenance therapy

Most patients identified with vitamin B12 deficiency require lifelong maintenance therapy with once-daily oral cyanocobalamin, or once-monthly parenteral cyanocobalamin. Oral cyanocobalamin is generally well tolerated for maintenance. Parenteral cyanocobalamin is often reserved for those who cannot take daily pills or have documented failure to oral therapy. It may also be considered when there are concerns about adherence to oral vitamin B12 replacement therapy.[98]

Some clinicians may attempt to lower the effective dose of maintenance oral cyanocobalamin. Periodic monitoring after replacement may be able to identify patients who may maintain serum levels with oral doses <1000 micrograms/day.[99] However, absorption may be variable, and some patients may experience less than maximal clinical and laboratory response with oral cyanocobalamin doses <1000 micrograms/day.[100] [101] [102]

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute (summary)

symptomatic		
severe symptoms	**1st**	**parenteral cyanocobalamin or hydroxocobalamin**
	plus	**referral to neurologist and/or hematologist**
	adjunct	**blood transfusion ± low-dose diuretic**
	adjunct	**oral folic acid**
	plus	**lifelong oral or parenteral cyanocobalamin or parenteral hydroxocobalamin**
mild to moderate symptoms	**1st**	**oral or parenteral cyanocobalamin or parenteral hydroxocobalamin**
	plus	**lifelong oral or parenteral cyanocobalamin or parenteral hydroxocobalamin**
asymptomatic or borderline deficiency		
patients aged >65 years with poor diet	**1st**	**dietary supplementation + multivitamins**
	2nd	**lifelong oral or parenteral cyanocobalamin or parenteral hydroxocobalamin**
vegan or strict vegetarian diet	**1st**	**dietary supplementation + multivitamins**
	2nd	**lifelong oral or parenteral cyanocobalamin or parenteral hydroxocobalamin**
with chronic gastrointestinal illness	**1st**	**parenteral cyanocobalamin or hydroxocobalamin**
after bariatric surgery	**1st**	**oral, parenteral, or intranasal cyanocobalamin or parenteral hydroxocobalamin**

MANAGEMENT

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Acute

symptomatic

severe symptoms

1st **parenteral cyanocobalamin or hydroxocobalamin**

Primary options

» cyanocobalamin (vitamin B12): 1000 micrograms intramuscularly/subcutaneously once daily for 1-2 weeks, followed by 1000 micrograms once weekly for 1 month

OR

» hydroxocobalamin: 1000 micrograms intramuscularly three times weekly for 2 weeks, followed by 1000 micrograms once every 3 months

» Patients with severe hematologic (pancytopenia and marked symptomatic anemia) or neurologic (subacute combined spinal degeneration, dementia, or cognitive impairment) symptoms of vitamin B12 deficiency require hospital admission and acute and urgent treatment.[90]

» An acute regimen of parenteral cyanocobalamin is given daily for 1 to 2 weeks, and then once a week for up to 1 month, until significant reticulocytosis is seen in the marrow.[91]

» Brisk bone marrow reticulocytosis can be measured in 1-2 weeks as a response to treatment. Other markers of deficiency, including methylmalonic acid, homocysteine, and mean corpuscular volume, should normalize in 8 weeks with adequate treatment.

» In Europe, hydroxocobalamin is more commonly used than cyanocobalamin. Hydroxocobalamin is retained longer in the body than cyanocobalamin, but superiority to cyanocobalamin has not been established in clinical trials.

plus **referral to neurologist and/or hematologist**

Treatment recommended for ALL patients in selected patient group

Acute

» Patients with severe neurologic symptoms may require neurologic and psychogeriatric referral and evaluation while commencing the acute parenteral treatment regimen. In some cases, neurologic symptoms may be irreversible despite serum vitamin B12 levels returning to normal.

» Patients with symptomatic anemia and pancytopenia require hospital admission and hematologic specialist referral.

» Pregnant women should be managed in consultation with their obstetrician.

adjunct **blood transfusion ± low-dose diuretic**

Treatment recommended for SOME patients in selected patient group

Primary options

» bumetanide: 0.5 to 2 mg orally/intravenously once or twice daily initially, increase according to response, maximum 10 mg/day

» Patients with symptomatic anemia and pancytopenia require hospital admission and hematologic specialist referral and, rarely, may require red blood cell (RBC) transfusion.

» If there are signs of congestive cardiac failure, cardiac monitoring is advised and packed RBCs should be given together with low-dose diuretic therapy.

» Diuretics should generally be avoided in pregnancy unless the benefits outweigh the risks, and only under specialist guidance.

adjunct **oral folic acid**

Treatment recommended for SOME patients in selected patient group

Primary options

» folic acid (vitamin B9): 1 mg orally once daily

» Folate supplementation can help reverse the hematologic abnormalities.

plus **lifelong oral or parenteral cyanocobalamin or parenteral hydroxocobalamin**

Treatment recommended for ALL patients in selected patient group

Primary options

Acute

» cyanocobalamin (vitamin B12): 1000 micrograms orally once daily

Secondary options

» cyanocobalamin (vitamin B12): 1000 micrograms intramuscularly/subcutaneously once monthly

OR

» hydroxocobalamin: 1000 micrograms intramuscularly once every 3 months

» Most patients identified with vitamin B12 deficiency require lifelong maintenance therapy with once-daily oral cyanocobalamin or once-monthly parenteral cyanocobalamin.

» Oral cyanocobalamin is generally well tolerated for maintenance therapy. Parenteral cyanocobalamin is often reserved for those who cannot take daily pills or have documented failure to oral therapy. It may also be considered when there are concerns about adherence to oral vitamin B12 replacement therapy.[98]

» Some clinicians may attempt to lower the effective dose of maintenance oral cyanocobalamin. Periodic monitoring after replacement may be able to identify patients who may maintain serum levels with oral doses <1000 micrograms/day.[99] However, absorption may be variable, and some patients may experience less than maximal clinical and laboratory response with oral cyanocobalamin doses <1000 micrograms/day.[100] [101] [102]

» Absorption can be maximized by administration on an empty stomach.

» A response with daily oral cyanocobalamin should be seen within 8 weeks. If serum vitamin B12 does not significantly rise after this time, clinicians should switch to parenteral cyanocobalamin (if not already used) or consider other causes.

» In Europe, hydroxocobalamin is more commonly used than cyanocobalamin. Hydroxocobalamin is retained longer in the body than cyanocobalamin, but superiority to cyanocobalamin has not been established in clinical trials.

mild to moderate symptoms — **1st** — **oral or parenteral cyanocobalamin or parenteral hydroxocobalamin**

Acute

Primary options

» cyanocobalamin (vitamin B12): 1000 micrograms orally once daily; 1000 micrograms intramuscularly/subcutaneously once monthly

OR

» hydroxocobalamin: 1000 micrograms intramuscularly once every 3 months

» Treatment of patients with mild to moderate symptoms of vitamin B12 deficiency (e.g., mild anemia, dysesthesia/paresthesias, polyneuropathy, depression) is with once-daily oral cyanocobalamin or once-monthly parenteral cyanocobalamin, depending on clinician preference.

» In patients treated with oral cyanocobalamin, a response should be seen within 8 weeks. If serum vitamin B12 does not significantly rise after this time, clinicians should switch to parenteral cyanocobalamin (if not already used) or consider other causes.

» In Europe, hydroxocobalamin is more commonly used than cyanocobalamin. Hydroxocobalamin is retained longer in the body than cyanocobalamin, but superiority to cyanocobalamin has not been established in clinical trials.

plus **lifelong oral or parenteral cyanocobalamin or parenteral hydroxocobalamin**

Treatment recommended for ALL patients in selected patient group

Primary options

» cyanocobalamin (vitamin B12): 1000 micrograms orally once daily

Secondary options

» cyanocobalamin (vitamin B12): 1000 micrograms intramuscularly/subcutaneously once monthly

OR

» hydroxocobalamin: 1000 micrograms intramuscularly once every 3 months

» Most patients identified with vitamin B12 deficiency require lifelong maintenance therapy

Acute

with once-daily oral cyanocobalamin or once-monthly parenteral cyanocobalamin.

» Oral cyanocobalamin is generally well tolerated for maintenance therapy. Parenteral cyanocobalamin is often reserved for those who cannot take daily pills or have documented failure to oral therapy. It may also be considered when there are concerns about adherence to oral vitamin B12 replacement therapy.[98]

» Some clinicians may attempt to lower the effective dose of maintenance oral cyanocobalamin. Periodic monitoring after replacement may be able to identify patients who may maintain serum levels with oral doses <1000 micrograms/day.[99] However, absorption may be variable, and some patients may experience less than maximal clinical and laboratory response with oral cyanocobalamin doses <1000 micrograms/day.[100] [101] [102]

» Absorption can be maximized by administration on an empty stomach.

» A response with daily oral cyanocobalamin should be seen within 8 weeks. If serum vitamin B12 does not significantly rise after this time, clinicians should switch to parenteral cyanocobalamin (if not already used) or consider other causes.

» In Europe, hydroxocobalamin is more commonly used than cyanocobalamin. Hydroxocobalamin is retained longer in the body than cyanocobalamin, but superiority to cyanocobalamin has not been established in clinical trials.

asymptomatic or borderline deficiency

patients aged >65 years with poor diet — **1st** — **dietary supplementation + multivitamins**

» About 5% to 35% of older people have evidence of vitamin B12 deficiency.[11] [12] [13] [14] [15] [16]

» Low serum vitamin B12 (<200 picograms/mL) may not be associated with symptoms. But dietary advice on the importance of eating animal-derived foods (such as meat, fish, eggs, and milk), and taking multivitamin supplements, is recommended as first-line treatment in this group.

Acute

» Combined diet and multivitamins should meet the recommended dietary allowance of 2.4 micrograms/day.[58]

2nd **lifelong oral or parenteral cyanocobalamin or parenteral hydroxocobalamin**

Primary options

» cyanocobalamin (vitamin B12): 1000 micrograms orally once daily

Secondary options

» cyanocobalamin (vitamin B12): 1000 micrograms intramuscularly/subcutaneously once monthly

OR

» hydroxocobalamin: 1000 micrograms intramuscularly once every 3 months

» If diet and multivitamin supplements do not help, or if the diet cannot be improved, cyanocobalamin treatment is advised.

» Most patients identified with vitamin B12 deficiency require lifelong maintenance therapy with once-daily oral cyanocobalamin or once-monthly parenteral cyanocobalamin.

» Oral cyanocobalamin is generally well tolerated for maintenance therapy. Parenteral cyanocobalamin is often reserved for those who cannot take daily pills or have documented failure to high-dose oral therapy. It may also be considered when there are concerns about adherence to oral vitamin B12 replacement therapy.[98]

» Some clinicians may attempt to lower the effective dose of maintenance oral cyanocobalamin. Periodic monitoring after replacement may be able to identify patients who may maintain serum levels with oral doses <1000 micrograms/day.[99] However, absorption may be variable, and some patients may experience less than maximal clinical and laboratory response with oral cyanocobalamin doses <1000 micrograms/day.[100] [101] [102]

» Absorption can be maximized by administration on an empty stomach.

» A response with daily oral cyanocobalamin should be seen within 8 weeks. If serum vitamin B12 does not significantly rise after this time, clinicians should switch to parenteral

Acute

cyanocobalamin (if not already used) or consider other causes.

» In Europe, hydroxocobalamin is more commonly used than cyanocobalamin. Hydroxocobalamin is retained longer in the body than cyanocobalamin, but superiority to cyanocobalamin has not been established in clinical trials.

vegan or strict vegetarian diet

1st **dietary supplementation + multivitamins**

» Vegans or strict vegetarians should be counseled to supplement their diet with appropriate vitamin B12-fortified foods and multivitamin supplements in order to meet the recommended dietary allowance of 2.4 micrograms/day.[58] [93]

» Pregnant and breast-feeding women who have a strict vegetarian or vegan diet should be counseled about adequate intake of vitamin B12 and supplementation.[103] Breast-feeding women who adhere to a vegan diet will only provide adequate vitamin B12 for her infant if the mother satisfies vitamin B12 requirements through supplementation.[97]

2nd **lifelong oral or parenteral cyanocobalamin or parenteral hydroxocobalamin**

Primary options

» cyanocobalamin (vitamin B12): 1000 micrograms orally once daily

Secondary options

» cyanocobalamin (vitamin B12): 1000 micrograms intramuscularly/subcutaneously once monthly

OR

» hydroxocobalamin: 1000 micrograms intramuscularly once every 3 months

» Lifelong maintenance treatment with once-daily oral cyanocobalamin or once-monthly parenteral cyanocobalamin is advised.

» Oral cyanocobalamin is generally well tolerated for maintenance therapy. Parenteral cyanocobalamin is often reserved for those who cannot take daily pills or have documented failure to oral therapy. It may also be considered when there are concerns about adherence to oral vitamin B12 replacement therapy.[98]

Acute

» Some clinicians may attempt to lower the effective dose of maintenance oral cyanocobalamin. Periodic monitoring after replacement may be able to identify patients who may maintain serum levels with oral doses <1000 micrograms/day.[99] However, absorption may be variable, and some patients may experience less than maximal clinical and laboratory response with oral cyanocobalamin doses <1000 micrograms/day.[100] [101] [102]

» Absorption can be maximized by administration on an empty stomach.

» A response with daily oral cyanocobalamin should be seen within 8 weeks. If serum vitamin B12 does not significantly rise after this time, clinicians should switch to parenteral cyanocobalamin (if not already used) or consider other causes.

» In Europe, hydroxocobalamin is more commonly used than cyanocobalamin. Hydroxocobalamin is retained longer in the body than cyanocobalamin, but superiority to cyanocobalamin has not been established in clinical trials.

with chronic gastrointestinal illness — **1st** — **parenteral cyanocobalamin or hydroxocobalamin**

Primary options

» cyanocobalamin (vitamin B12): 1000 micrograms intramuscularly/subcutaneously once monthly

OR

» hydroxocobalamin: 1000 micrograms intramuscularly once every 3 months

» Patients with a chronic gastrointestinal (GI) illness that can cause malabsorption or inadequate absorption (e.g., pernicious anemia, Crohn disease, celiac disease) or who have undergone gastric surgery or terminal ileectomy should be treated with parenteral cyanocobalamin.[1] [94]

» In Europe, hydroxocobalamin is more commonly used than cyanocobalamin. Hydroxocobalamin is retained longer in the body than cyanocobalamin, but superiority to cyanocobalamin has not been established in clinical trials.

Acute

after bariatric surgery	**1st**	**oral, parenteral, or intranasal cyanocobalamin or parenteral hydroxocobalamin** **Primary options** » cyanocobalamin (vitamin B12): 350-1000 micrograms orally once daily; or 1000 micrograms intramuscularly/subcutaneously once monthly; or 3000 micrograms intramuscularly/subcutaneously every 6 months; or 500 micrograms intranasally once weekly **OR** » hydroxocobalamin: 1000 micrograms intramuscularly once every 3 months » Patients who have had bariatric surgery may not be able to adequately maintain serum vitamin B12 levels with multivitamins; therefore, oral, parenteral, or intranasal cyanocobalamin should be given.[74] [95] An oral multivitamin supplement optimized for bariatric surgery has shown potential benefit in reducing vitamin deficiencies following Roux-en-Y gastric bypass surgery, but the evidence is limited.[96] » In Europe, hydroxocobalamin is more commonly used than cyanocobalamin. Hydroxocobalamin is retained longer in the body than cyanocobalamin, but superiority to cyanocobalamin has not been established in clinical trials.

Primary prevention

The recommended dietary allowance (RDA) for vitamin B12 is 2.4 micrograms/day in men and women aged 14 years and above.[58] During pregnancy and lactation, the RDA is 2.6 and 2.8 micrograms/day, respectively.[58] [59]

Most vitamin B12 is obtained through ingestion of meat and dairy products, and body stores of vitamin B12 remain for years. Food fortification policies may reduce risk of vitamin B12 deficiency.[60]

Countries with a high prevalence of vitamin B12 depletion and deficiency may consider the inclusion of vitamin B12 when staples are fortified with folic acid. This may help to prevent unintended consequences of excess folic acid consumption.[61] [62]

Vegans and strict vegetarians may be at risk of vitamin B12 deficiency, and should supplement their diet with vitamin B12-fortified foods or a multivitamin containing a minimum of 2.4 micrograms of vitamin B12 per day. Those with a history of gastric bypass surgery or gastrectomy should supplement their diet with additional vitamin B12.[63]

Secondary prevention

Vegans, strict vegetarians, and older people are at risk of vitamin B12 deficiency without multivitamin supplementation or vitamin B12-fortified foods. Optimal dosing of vitamin B12 supplementation is uncertain, but older people may need oral dosages of >500 micrograms/day for optimal absorption.[115] Most vegans and strict vegetarians should absorb free vitamin B12 in standard multivitamins or fortified foods without difficulty, and minimal target intake should meet the recommended dietary allowance (2.4 micrograms/day). In vegans and vegetarians with marginal vitamin B12 stores, one study demonstrated improvement of stores with 50 micrograms/day of sublingual vitamin B12 or 2000 micrograms/week of sublingual vitamin B12.[93] The results support the use of a sublingual supplement at low doses in this population.[93]

In patients with diagnosed pernicious anemia (due to lack of intrinsic factor), endoscopic follow-up is advised in view of their increased risk of developing gastric cancer. A two to threefold excess risk of gastric cancer has been noted in patients with pernicious anemia.[81]

Patient discussions

The clinician should ensure that the patient is followed up as clinically indicated because some patients may not have complete resolution of neurologic symptoms, despite adequate treatment. It should be explained that treatment may only prevent further neuropsychiatric complications.

Patients should be advised about the importance of eating animal-derived foods, such as fish, meat, eggs, and milk, or taking multivitamin supplements.[58]

Specific advice for patients on plant-based diets (including vegans and strict vegetarians) includes taking a daily vitamin B12 supplement with food and choosing food products that are labeled as being fortified with vitamin B12.[114]

Monitoring

Monitoring

Patients with vitamin B12 deficiency should have close follow-up to confirm the diagnosis and to determine response to treatment. In patients with minimal symptoms and without anemia causing hemodynamic compromise, this can generally be done 2 to 3 months from initiation of treatment. Follow-up serum vitamin B12 levels, methylmalonic acid levels, or homocysteine levels should be measured to determine response to treatment.

European Society for Clinical Nutrition and Metabolism guidelines recommend a minimum of annual assessment for individuals at risk of vitamin B12 deficiency or those receiving treatment.[59]

Incomplete response should alert the clinician to look for other causes of macrocytic anemia and/or neurologic disease.

FOLLOW UP

Complications

Complications	Timeframe	Likelihood
neurologic deficits	**long term**	**high**
Those inadequately treated for vitamin B12 deficiency can have progressive neurologic damage.		
hematologic deficits	**long term**	**high**
Those inadequately treated for vitamin B12 deficiency can have progressive anemia, leukopenia, and thrombocytopenia.		
gastric cancer	**long term**	**low**
Gastric cancer is a long-term complication of untreated pernicious anemia (with antibodies to intrinsic factor). A two to threefold excess risk of gastric cancer has been noted in patients with pernicious anemia.[81]		
psychiatric conditions	**variable**	**high**
Vitamin B12 deficiency may manifest with psychiatric symptoms such as cognitive impairment and irritability, or with conditions including dementia and depression.[43] [59] In one prospective study of adults ages ≥50 years, those with deficient to low vitamin B12 status were 51% more likely to develop depressive symptoms over 4 years.[113] The potential for improvement of depressive symptoms in patients receiving vitamin B12 supplementation may differ between those with recent onset and those with more advanced neurologic disorders.[109] [110] There is no clear evidence that vitamin B12 supplementation alone improves dementia or cognitive decline, although some studies suggest that supplementation with a vitamin B complex or folic acid combined with vitamin B12 may slow progression and improve symptoms.[7] [8] [9] [112]		
low birth weight and preterm delivery (vitamin B12 deficiency during pregnancy)	**variable**	**low**
One systematic review found that vitamin B12 deficiency is common during pregnancy and that levels of vitamin B12 decrease from the first to the third trimester.[30] Vitamin B12 deficiency in pregnancy may be associated with an increased risk for preterm delivery, lower birth weight, and lower infant levels of vitamin B12.[56] [57]		

Prognosis

Vitamin B12 deficiency can cause devastating neurologic disease and severe hematologic disorders. Early diagnosis and prompt treatment may halt progression and reverse neurologic disease.[42] Unfortunately many cases are irreversible and clinical disease may not respond to adequate therapy.[75] Early diagnosis in the near-asymptomatic stage can be critical in preventing permanent neurologic damage.

Megaloblastic anemia

Prompt treatment in patients with megaloblastic anemia due to vitamin B12 deficiency can completely reverse the process. Brisk reticulocytosis occurs within 1 to 2 weeks of initiating treatment.

Subacute combined spinal degeneration

Treatment with vitamin B12 generally leads to clinical (and magnetic resonance imaging) improvement of subacute combined spinal degeneration, and can halt progression of disease. However, only a few patients will have complete resolution with vitamin B12 replacement.[75]

Other neurologic disease

Vitamin B12 treatment may improve peripheral neuropathy.[107] [108] Treatment may not completely resolve the process.

The potential for improvement of depressive symptoms in patients receiving vitamin B12 supplementation may differ between those with recent onset and those with more advanced neurologic disorders.[109] [110]

There is no clear evidence that vitamin B12 supplementation improves dementia or cognitive decline, although some evidence suggests that supplementation with a vitamin B complex or folic acid combined with vitamin B12 may slow progression of cognitive decline and improve symptoms.[7][9] [111][112]

Diagnostic guidelines

International

Cobalamin (vitamin B12) and folate deficiency (https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/vitamin-b12) [64]

Published by: Guidelines and Protocols Advisory Committee, British Columbia **Last published:** 2023

Diagnosis of B12 and folate deficiency (https://b-s-h.org.uk/guidelines) [1]

Published by: British Society for Haematology **Last published:** 2014

Treatment guidelines

International

Dietary supplement fact sheet: vitamin B12 (https://ods.od.nih.gov/factsheets/VitaminB12-HealthProfessional) [58]

Published by: Office of Dietary Supplements, National Institutes of Health **Last published:** 2022

Dietary guidelines for Americans 2020-2025 (https://health.gov/our-work/food-nutrition/current-dietary-guidelines) [104]

Published by: US Department of Health and Human Services; US Department of Agriculture **Last published:** 2020

Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient - 2019 update (https://asmbs.org/resource-categories/guidelines-recommendations) [74]

Published by: American Association of Clinical Endocrinologists; Obesity Society; American Society for Metabolic & Bariatric Surgery **Last published:** 2019

Cobalamin (vitamin B12) and folate deficiency (https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/vitamin-b12) [105]

Published by: Guidelines and Protocols Advisory Committee, British Columbia **Last published:** 2023

ESPEN micronutrient guideline (https://www.espen.org/guidelines-home/espen-guidelines) [59]

Published by: European Society for Clinical Nutrition and Metabolism **Last published:** 2022

ESPEN practical guideline: Clinical nutrition in inflammatory bowel disease (https://www.espen.org/guidelines-home/espen-guidelines) [94]

Published by: European Society for Clinical Nutrition and Metabolism **Last published:** 2020

Diagnosis of B12 and folate deficiency (https://b-s-h.org.uk/guidelines) [1]

Published by: British Society for Haematology **Last published:** 2014

Nutrient reference values for Australia and New Zealand (https://www.nhmrc.gov.au/about-us/publications/nutrient-reference-values-australia-and-new-zealand-including-recommended-dietary-intakes) [106]

Published by: Australian Government National Health and Medical Research Council and New Zealand Ministry for Health **Last published:** 2017

Online resources

1. CDC: HIV - laboratory tests (https://www.cdc.gov/hiv/testing/laboratorytests.html) *(external link)*

Key articles

- Devalia V, Hamilton MS, Molloy AM; British Committee for Standards in Haematology. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. Br J Haematol. 2014 Aug;166(4):496-513. Full text (http://onlinelibrary.wiley.com/doi/10.1111/bjh.12959/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/24942828?tool=bestpractice.bmj.com)
- Snow CF. Laboratory diagnosis of vitamin B12 and folate deficiency: a guide for the primary care physician. Arch Intern Med. 1999 Jun 28;159(12):1289-98. Full text (http://archinte.ama-assn.org/cgi/content/full/159/12/1289) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10386505?tool=bestpractice.bmj.com)
- Stabler SP. Clinical practice. Vitamin B12 deficiency. N Engl J Med. 2013 Jan 10;368(2):149-60. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23301732?tool=bestpractice.bmj.com)
- National Institutes of Health, Office of Dietary Supplements. Dietary supplement fact sheet: vitamin B12. 2022 [internet publication]. Full text (https://health.gov/our-work/food-nutrition/current-dietary-guidelines)
- Guidelines and Protocols Advisory Committee, British Columbia. Cobalamin (vitamin B12) and folate deficiency. Jan 2023 [internet publication]. Full text (https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/vitamin-b12)

References

1. Devalia V, Hamilton MS, Molloy AM; British Committee for Standards in Haematology. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. Br J Haematol. 2014 Aug;166(4):496-513. Full text (http://onlinelibrary.wiley.com/doi/10.1111/bjh.12959/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/24942828?tool=bestpractice.bmj.com)
2. Snow CF. Laboratory diagnosis of vitamin B12 and folate deficiency: a guide for the primary care physician. Arch Intern Med. 1999 Jun 28;159(12):1289-98. Full text (http://archinte.ama-assn.org/cgi/content/full/159/12/1289) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10386505?tool=bestpractice.bmj.com)
3. Tavares J, Baptista B, Gonçalves B, et al. Pernicious anaemia with normal vitamin B12. Eur J Case Rep Intern Med. 2019;6(2):001045. Full text (https://www.ejcrim.com/index.php/EJCRIM/article/view/1045) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30931271?tool=bestpractice.bmj.com)
4. Shah DR, Daver N, Borthakur G, et al. Pernicious anemia with spuriously normal vitamin B12 level might be misdiagnosed as myelodysplastic syndrome. Clin Lymphoma Myeloma Leuk. 2014 Aug;14(4):e141-3. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/24630920?tool=bestpractice.bmj.com)

REFERENCES

5. Yang DT, Cook RJ. Spurious elevations of vitamin B12 with pernicious anemia. N Engl J Med. 2012 May 3;366(18):1742-3. Full text (https://www.nejm.org/doi/full/10.1056/NEJMc1201655) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22551146?tool=bestpractice.bmj.com)

6. Mazokopakis EE. Normal serum cobalamin levels do not exclude the diagnosis of pernicious anaemia: a case report. Fam Pract. 2020 Feb 19;37(1):1-3. Full text (https://academic.oup.com/fampra/article/37/1/1/5709531) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31953947?tool=bestpractice.bmj.com)

7. Wang Z, Zhu W, Xing Y, et al. B vitamins and prevention of cognitive decline and incident dementia: a systematic review and meta-analysis. Nutr Rev. 2022 Mar 10;80(4):931-49. Full text (https://academic.oup.com/nutritionreviews/article/80/4/931/6357328?login=false) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34432056?tool=bestpractice.bmj.com)

8. Chen H, Liu S, Ge B, et al. Effects of folic acid and vitamin B12 supplementation on cognitive impairment and inflammation in patients with Alzheimer's disease: a randomized, single-blinded, placebo-controlled trial. J Prev Alzheimers Dis. 2021;8(3):249-56. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34101780?tool=bestpractice.bmj.com)

9. Gil Martínez V, Avedillo Salas A, Santander Ballestín S. Vitamin supplementation and dementia: a systematic review. Nutrients. 2022 Feb 28;14(5):1033. Full text (https://www.mdpi.com/2072-6643/14/5/1033) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/35268010?tool=bestpractice.bmj.com)

10. Tucker KL, Rich S, Rosenberg I, et al. Plasma vitamin B-12 concentrations relate to intake source in the Framingham Offspring study. Am J Clin Nutr. 2000 Feb;71(2):514-22. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10648266?tool=bestpractice.bmj.com)

11. Sukumar N, Saravanan P. Investigating vitamin B12 deficiency. BMJ. 2019 May 10;365:l1865. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31076395?tool=bestpractice.bmj.com)

12. Pennypacker LC, Allen RH, Kelly JP, et al. High prevalence of cobalamin deficiency in elderly outpatients. J Am Geriatr Soc. 1992 Dec;40(12):1197-204. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/1447433?tool=bestpractice.bmj.com)

13. Clarke R, Grimley Evans J, Schneede J, et al. Vitamin B12 and folate deficiency in later life. Age Ageing. 2004 Jan;33(1):34-41. Full text (http://ageing.oxfordjournals.org/cgi/reprint/33/1/34) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/14695861?tool=bestpractice.bmj.com)

14. Andres E, Loukili NH, Noel E, et al. Vitamin B12 (cobalamin) deficiency in elderly patients. CMAJ. 2004 Aug 3;171(3):251-9. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC490077) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15289425?tool=bestpractice.bmj.com)

15. Pfisterer KJ, Sharratt MT, Heckman GG, et al. Vitamin B12 status in older adults living in Ontario long-term care homes: prevalence and incidence of deficiency with supplementation as a protective factor. Appl Physiol Nutr Metab. 2016 Feb;41(2):219-22. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26781161?tool=bestpractice.bmj.com)

16. Wong CW, Ip CY, Leung CP, et al. Vitamin B12 deficiency in the institutionalized elderly: A regional study. Exp Gerontol. 2015 Sep;69:221-5. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26122132?tool=bestpractice.bmj.com)

17. Mineva EM, Sternberg MR, Bailey RL, et al. Fewer US adults had low or transitional vitamin B12 status based on the novel combined indicator of vitamin B12 status compared with individual, conventional markers, NHANES 1999-2004. Am J Clin Nutr. 2021 Sep 1;114(3):1070-79. Full text (https://www.sciencedirect.com/science/article/pii/S0002916522004300?via%3Dihub) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33963731?tool=bestpractice.bmj.com)

18. Hunt A, Harrington D, Robinson S. Vitamin B12 deficiency. BMJ. 2014 Sep 4;349:g5226. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/25189324?tool=bestpractice.bmj.com)

19. Allen LH. How common is vitamin B-12 deficiency? Am J Clin Nutr. 2009 Feb;89(2):693S-6S. Full text (https://academic.oup.com/ajcn/article/89/2/693S/4596795) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/19116323?tool=bestpractice.bmj.com)

20. Björkegren K, Svärdsudd K. Serum cobalamin, folate, methylmalonic acid and total homocysteine as vitamin B12 and folate tissue deficiency markers amongst elderly Swedes - a population-based study. J Intern Med. 2001 May;249(5):423-32. Full text (https://onlinelibrary.wiley.com/doi/full/10.1046/j.1365-2796.2001.00819.x) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/11350566?tool=bestpractice.bmj.com)

21. Yajnik CS, Deshpande SS, Lubree HG, et al. Vitamin B12 deficiency and hyperhomocysteinemia in rural and urban Indians. J Assoc Physicians India. 2006 Oct;54:775-82. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17214273?tool=bestpractice.bmj.com)

22. Fakhrzadeh H, Ghotbi S, Pourebrahim R, et al. Total plasma homocysteine, folate, and vitamin B12 status in healthy Iranian adults: the Tehran homocysteine survey (2003-2004)/a cross-sectional population based study. BMC Public Health. 2006 Feb 13;6:29. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1403764) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16472406?tool=bestpractice.bmj.com)

23. Loikas S, Koskinen P, Irjala K, et al. Vitamin B12 deficiency in the aged: a population-based study. Age Ageing. 2007 Mar;36(2):177-83. Full text (http://ageing.oxfordjournals.org/cgi/content/full/36/2/177) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17189285?tool=bestpractice.bmj.com)

24. Madhari RS, Boddula S, Ravindranadh P, et al. High dietary micronutrient inadequacy in peri-urban school children from a district in South India: Potential for staple food fortification and nutrient supplementation. Matern Child Nutr. 2020 Dec;16 Suppl 3:e13065. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7752122) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33347729?tool=bestpractice.bmj.com)

25. Pawlak R, Parrott SJ, Raj S, et al. How prevalent is vitamin B(12) deficiency among vegetarians? Nutr Rev. 2013 Feb;71(2):110-7. Full text (https://academic.oup.com/nutritionreviews/article/71/2/110/1940320?login=false) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23356638?tool=bestpractice.bmj.com)

REFERENCES

26. Herrmann W, Schorr H, Obeid R, et al. Vitamin B-12 status, particularly holotranscobalamin II and methylmalonic acid concentrations, and hyperhomocysteinemia in vegetarians. Am J Clin Nutr. 2003 Jul;78(1):131-6. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12816782?tool=bestpractice.bmj.com)

27. Weng TC, Chang CH, Dong YH, et al. Anaemia and related nutrient deficiencies after Roux-en-Y gastric bypass surgery: a systematic review and meta-analysis. BMJ Open. 2015 Jul 16;5(7):e006964. Full text (http://bmjopen.bmj.com/content/5/7/e006964.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26185175?tool=bestpractice.bmj.com)

28. Schijns W, Homan J, van der Meer L, et al. Efficacy of oral compared with intramuscular vitamin B-12 supplementation after Roux-en-Y gastric bypass: a randomized controlled trial. Am J Clin Nutr. 2018 Jul 1;108(1):6-12. Full text (https://www.sciencedirect.com/science/article/pii/S0002916522029057?via%3Dihub) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29931179?tool=bestpractice.bmj.com)

29. Rashid S, Meier V, Patrick H. Review of vitamin B12 deficiency in pregnancy: a diagnosis not to miss as veganism and vegetarianism become more prevalent. Eur J Haematol. 2021 Apr;106(4):450-5. Full text (https://onlinelibrary.wiley.com/doi/10.1111/ejh.13571) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33341967?tool=bestpractice.bmj.com)

30. Sukumar N, Rafnsson SB, Kandala NB, et al. Prevalence of vitamin B-12 insufficiency during pregnancy and its effect on offspring birth weight: a systematic review and meta-analysis. Am J Clin Nutr. 2016 May;103(5):1232-51. Full text (http://ajcn.nutrition.org/content/103/5/1232.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27076577?tool=bestpractice.bmj.com)

31. Jung SB, Nagaraja V, Kapur A, et al. Association between vitamin B12 deficiency and long-term use of acid-lowering agents: a systematic review and meta-analysis. Intern Med J. 2015 Apr;45(4):409-16. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/25583062?tool=bestpractice.bmj.com)

32. Chapman LE, Darling AL, Brown JE, et al. Association between metformin and vitamin B12 deficiency in patients with type 2 diabetes: a systematic review and meta-analysis. Diabetes Metab. 2016 Nov;42(5):316-27. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27130885?tool=bestpractice.bmj.com)

33. Marino MC, de Olivera CA, Rocha AM, et al. Longterm effect of Helicobacter pylori eradication on plasma homocysteine in elderly patients with cobalamin deficiency. Gut. 2007 Apr;56(4):469-74. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1856853) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17005765?tool=bestpractice.bmj.com)

34. Kaptan K, Beyan C, Ural AU, et al. Helicobacter pylori - is it a novel causative agent in vitamin B12 deficiency? Arch Intern Med. 2000 May 8;160(9):1349-53. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/10809040?tool=bestpractice.bmj.com)

35. Lewerin C, Jacobsson S, Lindstedt G, et al. Serum biomarkers for atrophic gastritis and antibodies against Helicobacter pylori in the elderly: implications for vitamin B12, folic acid and iron status and response to oral vitamin therapy. Scand J Gastroenterol. 2008;43(9):1050-6. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/18609169?tool=bestpractice.bmj.com)

36. Afsar MNA, Jhinu ZN, Bhuiyan MAI, et al. Helicobacter pylori infection and micronutrient deficiency in pregnant women: a systematic review and meta-analysis. BMJ Open Gastroenterol. 2020

Oct;7(1):e000490. Full text (https://bmjopengastro.bmj.com/content/7/1/e000490.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33093020?tool=bestpractice.bmj.com)

37. Aslan K, Bozdemir H, Unsal C, et al. The effect of anticonvulsant drugs on vitamin B12 metabolism. Int J Lab Hematol. 2008 Feb;30(1):26-35. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/18190464?tool=bestpractice.bmj.com)

38. Linnebank M, Moskau S, Semmler A, et al. Antiepileptic drugs interact with folate and vitamin B12 serum levels. Ann Neurol. 2011 Feb;69(2):352-9. Full text (http://www.zora.uzh.ch/id/eprint/43383/1/Main_r1_table_Annals_of_Neurology.pdf) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21246600?tool=bestpractice.bmj.com)

39. Paulus MC, Wijnhoven AM, Maessen GC, et al. Does vitamin B12 deficiency explain psychiatric symptoms in recreational nitrous oxide users? A narrative review. Clin Toxicol (Phila). 2021 Nov;59(11):947-55. Full text (https://www.tandfonline.com/doi/full/10.1080/15563650.2021.1938107) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34348072?tool=bestpractice.bmj.com)

40. Oussalah A, Julien M, Levy J, et al. Global burden related to nitrous oxide exposure in medical and recreational settings: a systematic review and individual patient data meta-analysis. J Clin Med. 2019 Apr 23;8(4):551. Full text (https://www.mdpi.com/2077-0383/8/4/551) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31018613?tool=bestpractice.bmj.com)

41. van Amsterdam JG, Nabben T, van den Brink W. Increasing recreational nitrous oxide use: should we worry? A narrative review. J Psychopharmacol. 2022 Aug;36(8):943-50. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/35678512?tool=bestpractice.bmj.com)

42. Stabler SP. Clinical practice. Vitamin B12 deficiency. N Engl J Med. 2013 Jan 10;368(2):149-60. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/23301732?tool=bestpractice.bmj.com)

43. Sahu P, Thippeswamy H, Chaturvedi SK. Neuropsychiatric manifestations in vitamin B12 deficiency. Vitam Horm. 2022;119:457-70. Full text (https://www.sciencedirect.com/science/article/abs/pii/S0083672922000012?via%3Dihub) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/35337631?tool=bestpractice.bmj.com)

44. Arias PM, Domeniconi EA, García M, et al. Micronutrient deficiencies after Roux-en-Y gastric bypass: long-term results. Obes Surg. 2020 Jan;30(1):169-73. Full text (https://link.springer.com/article/10.1007/s11695-019-04167-x) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31502183?tool=bestpractice.bmj.com)

45. Shankar P, Boylan M, Sriram K. Micronutrient deficiencies after bariatric surgery. Nutrition. 2010 Nov-Dec;26(11-12):1031-7. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/20363593?tool=bestpractice.bmj.com)

46. Thompson WG, Wrathell E. The relation between ileal resection and vitamin B12 absorption. Can J Surg. 1977 Sep;20(5):461-4. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/890622?tool=bestpractice.bmj.com)

47. Duerksen DR, Fallows G, Bernstein CN. Vitamin B12 malabsorption in patients with limited ileal resection. Nutrition. 2006 Nov-Dec;22(11-12):1210-3. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/17095407?tool=bestpractice.bmj.com)

48. Lederer AK, Hannibal L, Hettich M, et al. Vitamin B12 status upon short-term intervention with a vegan diet-a randomized controlled trial in healthy participants. Nutrients. 2019 Nov 18;11(11):2815. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6893687) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31752105?tool=bestpractice.bmj.com)

49. Mazokopakis EE, Starakis IK. Recommendations for diagnosis and management of metformin-induced vitamin B12 (Cbl) deficiency. Diabetes Res Clin Pract. 2012 Sep;97(3):359-67. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/22770998?tool=bestpractice.bmj.com)

50. Aroda VR, Edelstein SL, Goldberg RB, et al. Long-term metformin use and vitamin b12 deficiency in the diabetes prevention program outcomes study. J Clin Endocrinol Metab. 2016 Apr;101(4):1754-61. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4880159) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26900641?tool=bestpractice.bmj.com)

51. Yang W, Cai X, Wu H, et al. Associations between metformin use and vitamin B12 levels, anemia, and neuropathy in patients with diabetes: a meta-analysis. J Diabetes. 2019 Sep;11(9):729-43. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30615306?tool=bestpractice.bmj.com)

52. de Jager J, Kooy A, Lehert P, et al. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. BMJ. 2010 May 20;340:c2181. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2874129) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/20488910?tool=bestpractice.bmj.com)

53. Lam JR, Schneider JL, Zhao W, et al. Proton pump inhibitor and histamine 2 receptor antagonist use and vitamin B12 deficiency. JAMA. 2013 Dec 11;310(22):2435-42. Full text (http://jama.jamanetwork.com/article.aspx?articleid=1788456) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/24327038?tool=bestpractice.bmj.com)

54. Pflipsen MC, Oh RC, Saguil A, et al. The prevalence of vitamin B12 deficiency in patients with type 2 diabetes mellitus: a cross-sectional study. J Am Board Fam Med. 2009 Sep-Oct;22(5):528-34. Full text (http://www.jabfm.org/content/22/5/528.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/19734399?tool=bestpractice.bmj.com)

55. Kim J, Ahn CW, Fang S, et al. Association between metformin dose and vitamin B12 deficiency in patients with type 2 diabetes. Medicine (Baltimore). 2019 Nov;98(46):e17918. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6867725) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31725641?tool=bestpractice.bmj.com)

56. Finkelstein JL, Kurpad AV, Thomas T, et al. Vitamin B12 status in pregnant women and their infants in South India. Eur J Clin Nutr. 2017 Sep 12;71(9):1046-53. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28402324?tool=bestpractice.bmj.com)

57. Rogne T, Tielemans MJ, Chong MF, et al. Associations of maternal vitamin B12 concentration in pregnancy with the risks of preterm birth and low birth weight: a systematic review and meta-analysis of individual participant data. Am J Epidemiol. 2017 Feb 1;185(3):212-23. Full text

(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5390862) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28108470?tool=bestpractice.bmj.com)

58. National Institutes of Health, Office of Dietary Supplements. Dietary supplement fact sheet: vitamin B12. 2022 [internet publication]. Full text (https://health.gov/our-work/food-nutrition/current-dietary-guidelines)

59. Berger MM, Shenkin A, Schweinlin A, et al. ESPEN micronutrient guideline. Clin Nutr. 2022;41:1357-424. Full text (https://www.espen.org/files/ESPEN-Guidelines/ESPEN_micronutrient_guideline.pdf)

60. Das JK, Salam RA, Mahmood SB, et al. Food fortification with multiple micronutrients: impact on health outcomes in general population. Cochrane Database Syst Rev. 2019 Dec 18;12:CD011400. Full text (https://www.doi.org/10.1002/14651858.CD011400.pub2) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31849042?tool=bestpractice.bmj.com)

61. World Health Organization. WHO fortification of wheat flour with vitamins and minerals as a public health strategy. 2022 [internet publication]. Full text (https://www.who.int/publications/i/item/9789240043398)

62. Ismail S, Eljazzar S, Ganji V. Intended and unintended Bbenefits of folic acid fortification-a narrative review. Foods. 2023 Apr 11;12(8):1612. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10137700) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/37107407?tool=bestpractice.bmj.com)

63. Moore M, Hopkins J, Wainwright P. Primary care management of patients after weight loss surgery. BMJ. 2016 Mar 10;352:i945. Full text (https://www.doi.org/10.1136/bmj.i945) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26964556?tool=bestpractice.bmj.com)

64. Guidelines and Protocols Advisory Committee, British Columbia. Cobalamin (vitamin B12) and folate deficiency. Jan 2023 [internet publication]. Full text (https://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/vitamin-b12)

65. Hoey L, Strain JJ, McNulty H. Studies of biomarker responses to intervention with vitamin B-12: a systematic review of randomized controlled trials. Am J Clin Nutr. 2009 Jun;89(6):1981S-96S. Full text (https://academic.oup.com/ajcn/article/89/6/1981S/4596903) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/19403638?tool=bestpractice.bmj.com)

66. National Institute for Health and Care Excellence. Active B12 assay for diagnosing vitamin B12 deficiency. Sep 2015 [internet publication]. Full text (https://www.nice.org.uk/advice/mib40)

67. Miller JW, Garrod MG, Rockwood AL, et al. Measurement of total vitamin B12 and holotranscobalamin, singly and in combination, in screening for metabolic vitamin B12 deficiency. Clin Chem. 2006 Feb;52(2):278-85. Full text (http://www.clinchem.org/cgi/content/full/52/2/278) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16384886?tool=bestpractice.bmj.com)

68. Obeid R, Herrmann W. Holotranscobalamin in laboratory diagnosis of cobalamin deficiency compared to total cobalamin and methylmalonic acid. Clin Chem Lab Med. 2007;45(12):1746-50. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/18067452?tool=bestpractice.bmj.com)

REFERENCES

69. Valente E, Scott JM, Ueland PM, et al. Diagnostic accuracy of holotranscobalamin, methylmalonic acid, serum cobalamin, and other indicators of tissue vitamin b12 status in the elderly. Clin Chem. 2011 Jun;57(6):856-63. Full text (http://www.clinchem.org/content/57/6/856.full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/21482749?tool=bestpractice.bmj.com)

70. Muckerheide M. Therapeutic doses of vitamin B12 give false-positive values for intrinsic-factor-blocking antibodies. Clin Chem. 1984 Sep;30(9):1579. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/6467575?tool=bestpractice.bmj.com)

71. Stenman UH. False-positive tests for intrinsic-factor antibody. Lancet. 1976 Aug 21;2(7982):428. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/73896?tool=bestpractice.bmj.com)

72. Slingerland DW, Cardarelli JA, Burrows BA, et al. The utility of serum gastrin levels in assessing the significance of low serum vitamin B12 levels. Arch Intern Med. 1984 Jun;144(6):1167-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/6732375?tool=bestpractice.bmj.com)

73. Simundic AM, Bölenius K, Cadamuro J, et al. Joint EFLM-COLABIOCLI recommendation for venous blood sampling. Clin Chem Lab Med. 2018;56(12):2015-38. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30004902?tool=bestpractice.bmj.com)

74. Mechanick JI, Apovian C, Brethauer S, et al; American Association of Clinical Endocrinologists; Obesity Society; American Society for Metabolic & Bariatric Surgery. Clinical practice guidelines for the perioperative nutritional, metabolic, and nonsurgical support of the bariatric surgery patient - 2019 update. Endocr Pract. 2019 Dec;25(12):1346-59. Full text (https://linkinghub.elsevier.com/retrieve/pii/S1530-891X(20)42802-2) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31682518?tool=bestpractice.bmj.com)

75. Vasconcelos OM, Poehm EH, McCarter RJ, et al. Potential outcome factors in subacute combined degeneration: review of observational studies. J Gen Intern Med. 2006 Oct;21(10):1063-8. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1831618) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16970556?tool=bestpractice.bmj.com)

76. Lindenbaum J, Healton EB, Savage DG, et al. Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. N Engl J Med. 1988 Jun 30;318(26):1720-8. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/3374544?tool=bestpractice.bmj.com)

77. Savage DG, Lindenbaum J, Stabler SP, et al. Sensitivity of serum methylmalonic acid and total homocysteine determinations for diagnosing cobalamin and folate deficiencies. Am J Med. 1994 Mar;96(3):239-46. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8154512?tool=bestpractice.bmj.com)

78. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5th ed., text revision (DSM-5-TR). Washington, DC: American Psychiatric Publishing; 2022.

79. Centers for Disease Control and Prevention. Laboratory testing for the diagnosis of HIV infection: updated recommendations. June 2014 [internet publication]. Full text (https://stacks.cdc.gov/view/cdc/23447)

80. Wile DJ, Toth C. Association of metformin, elevated homocysteine, and methylmalonic acid levels and clinically worsened diabetic peripheral neuropathy. Diabetes Care. 2010 Jan;33(1):156-61. Full

text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2797962) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/19846797?tool=bestpractice.bmj.com)

81. Hsing AW, Hansson LE, McLaughlin JK, et al. Pernicious anemia and subsequent cancer: a population-based cohort study. Cancer. 1993 Feb 1;71(3):745-50. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/8431855?tool=bestpractice.bmj.com)

82. Sanz-Cuesta T, Escortell-Mayor E, Cura-Gonzalez I, et al. Oral versus intramuscular administration of vitamin B12 for vitamin B12 deficiency in primary care: a pragmatic, randomised, non-inferiority clinical trial (OB12). BMJ Open. 2020 Aug 20;10(8):e033687. Full text (https://www.doi.org/10.1136/bmjopen-2019-033687) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/32819927?tool=bestpractice.bmj.com)

83. Kuzminski AM, Del Giacco EJ, Allen RH, et al. Effective treatment of cobalamin deficiency with oral cobalamin. Blood. 1998 Aug 15;92(4):1191-8. Full text (http://www.bloodjournal.org/content/92/4/1191.long) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9694707?tool=bestpractice.bmj.com)

84. Berlin H, Berlin R, Brante G. Oral treatment of pernicious anemia with high doses of vitamin B12 without intrinsic factor. Acta Med Scand. 1968 Oct;184(4):247-58. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/5751528?tool=bestpractice.bmj.com)

85. Gomollón F, Gargallo CJ, Muñoz JF, et al. Oral cyanocobalamin is effective in the treatment of vitamin B12 deficiency in Crohn's disease. Nutrients. 2017 Mar 20;9(3):E308. Full text (https://www.mdpi.com/2072-6643/9/3/308/htm) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/28335526?tool=bestpractice.bmj.com)

86. Wang H, Li L, Qin LL, et al. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency. Cochrane Database Syst Rev. 2018 Mar 15;(3):CD004655. Full text (http://cochranelibrary-wiley.com/doi/10.1002/14651858.CD004655.pub3/full) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29543316?tool=bestpractice.bmj.com)

87. Sharabi A, Cohen E, Sulkes J, et al. Replacement therapy for vitamin B12 deficiency: comparison between the sublingual and oral route. Br J Clin Pharmacol. 2003 Dec;56(6):635-8. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1884303) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/14616423?tool=bestpractice.bmj.com)

88. Slot WB, Merkus FW, Van Deventer SJ, et al. Normalization of plasma vitamin B12 concentration by intranasal hydroxocobalamin in vitamin B12-deficient patients. Gastroenterology. 1997 Aug;113(2):430-3. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/9247460?tool=bestpractice.bmj.com)

89. Parry-Strong A, Langdana F, Haeusler S, et al. Sublingual vitamin B12 compared to intramuscular injection in patients with type 2 diabetes treated with metformin: a randomised trial. N Z Med J. 2016 Jun 10;129(1436):67-75. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27355231?tool=bestpractice.bmj.com)

REFERENCES

90. Carmel R. How I treat cobalamin (vitamin B12) deficiency. Blood. 2008 Sep 15;112(6):2214-21. Full text (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2532799) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/18606874?tool=bestpractice.bmj.com)

91. Butler CC, Vidal-Alaball J, Cannings-John R, et al. Oral vitamin B12 versus intramuscular vitamin B12 for vitamin B12 deficiency: a systematic review of randomized controlled trials. Fam Pract. 2006 Jun;23(3):279-85. Full text (https://academic.oup.com/fampra/article/23/3/279/476697) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/16585128?tool=bestpractice.bmj.com)

92. Jatoi S, Hafeez A, Riaz SU, et al. Low vitamin B12 levels: an underestimated cause of minimal cognitive impairment and dementia. Cureus. 2020 Feb 13;12(2):e6976. Full text (https://www.doi.org/10.7759/cureus.6976) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/32206454?tool=bestpractice.bmj.com)

93. Del Bo' C, Riso P, Gardana C, et al. Effect of two different sublingual dosages of vitamin B₁₂ on cobalamin nutritional status in vegans and vegetarians with a marginal deficiency: A randomized controlled trial. Clin Nutr. 2019 Apr;38(2):575-583. Full text (https://www.doi.org/10.1016/j.clnu.2018.02.008) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29499976?tool=bestpractice.bmj.com)

94. Bischoff SC, Escher J, Hébuterne X, et al. ESPEN practical guideline: clinical nutrition in inflammatory bowel disease. Clin Nutr. 2020 Mar;39(3):632-53. Full text (https://www.doi.org/10.1016/j.clnu.2019.11.002) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/32029281?tool=bestpractice.bmj.com)

95. Mahawar KK, Reid A, Graham Y, et al. Oral vitamin B12 supplementation after Roux-en-Y gastric bypass: a systematic review. Obes Surg. 2018 Jul;28(7):1916-23. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/29318504?tool=bestpractice.bmj.com)

96. Homan J, Schijns W, Aarts EO, et al. An optimized multivitamin supplement lowers the number of vitamin and mineral deficiencies three years after Roux-en-Y gastric bypass: a cohort study. Surg Obes Relat Dis. 2016 Mar-Apr;12(3):659-67. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/26947791?tool=bestpractice.bmj.com)

97. Procter SB, Campbell CG. Position of the Academy of Nutrition and Dietetics: nutrition and lifestyle for a healthy pregnancy outcome. J Acad Nutr Diet. 2014 Jul;114(7):1099-103. Full text (https://www.doi.org/10.1016/j.jand.2014.05.005) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/24956993?tool=bestpractice.bmj.com)

98. Iacobucci G. Consider intramuscular injections for older people with vitamin B(12) deficiency, says NICE. BMJ. 2023 Jul 11;382:1604. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/37433611?tool=bestpractice.bmj.com)

99. Andrès E, Dali-Youcef N, Vogel T, et al. Oral cobalamin (vitamin B(12)) treatment: an update. Int J Lab Hematol. 2009 Feb;31(1):1-8. Full text (https://onlinelibrary.wiley.com/doi/10.1111/j.1751-553X.2008.01115.x) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/19032377?tool=bestpractice.bmj.com)

100. Rajan S, Wallace JI, Brodkin KI, et al. Response of elevated methylmalonic acid to three dose levels of oral cobalamin in older adults. J Am Geriatr Soc. 2002 Nov;50(11):1789-95. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12410896?tool=bestpractice.bmj.com)

101. Eussen SJ, de Groot LC, Clarke R, et al. Oral cyanocobalamin supplementation in older people with vitamin B12 deficiency: a dose-finding trial. Arch Intern Med. 2005 May 23;165(10):1167-72. Full text (http://archinte.ama-assn.org/cgi/content/full/165/10/1167) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/15911731?tool=bestpractice.bmj.com)

102. Andrès E, Fothergill H, Mecili M. Efficacy of oral cobalamin (vitamin B12) therapy. Expert Opin Pharmacother. 2010 Feb;11(2):249-56. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/20088746?tool=bestpractice.bmj.com)

103. Beyer TL, Dryden RM. Basal cell carcinoma masquerading as ectropion. Case report. Arch Ophthalmol. 1988 Feb;106(2):170-1. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/3341967?tool=bestpractice.bmj.com)

104. US Department of Health and Human Services; US Department of Agriculture. Dietary guidelines for Americans 2020-2025. December 2020 [internet publication]. Full text (https://www.dietaryguidelines.gov/resources/2020-2025-dietary-guidelines-online-materials)

105. Guidelines and Protocols Advisory Committee. Cobalamin (vitamin B12) deficiency: investigation and management. May 2013 [internet publication]. Full text (http://www2.gov.bc.ca/gov/content/health/practitioner-professional-resources/bc-guidelines/vitamin-b12)

106. Nutrient Reference values for Australia and New Zealand. Australian Government National Health and Medical Research Council and New Zealand Ministry for Health. 2018 [internet publication]. Full text (https://www.nrv.gov.au/nutrients/vitamin-b12)

107. Stein J, Geisel J, Obeid R. Association between neuropathy and B-vitamins: a systematic review and meta-analysis. Eur J Neurol. 2021 Jun;28(6):2054-64. Full text (https://www.doi.org/10.1111/ene.14786) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33619867?tool=bestpractice.bmj.com)

108. Healton EB, Savage DG, Brust JC, et al. Neurologic aspects of cobalamin deficiency. Medicine (Baltimore). 1991 Jul;70(4):229-45. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/1648656?tool=bestpractice.bmj.com)

109. Markun S, Gravestock I, Jäger L, et al. Effects of vitamin B12 supplementation on cognitive function, depressive symptoms, and fatigue: a systematic review, meta-analysis, and meta-regression. Nutrients. 2021 Mar 12;13(3):923. Full text (https://www.doi.org/10.3390/nu13030923) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/33809274?tool=bestpractice.bmj.com)

110. Syed EU, Wasay M, Awan S. Vitamin B12 supplementation in treating major depressive disorder: a randomized controlled trial. Open Neurol J. 2013;7:44-8. Full text (https://www.doi.org/10.2174/1874205X01307010044) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/24339839?tool=bestpractice.bmj.com)

REFERENCES

111. Vogel T, Dali-Youcef N, Kaltenbach G, et al. Homocysteine, vitamin B12, folate and cognitive functions: a systematic and critical review of the literature. Int J Clin Pract. 2009 Jul;63(7):1061-7. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/19570123?tool=bestpractice.bmj.com)

112. McCleery J, Abraham RP, Denton DA, et al. Vitamin and mineral supplementation for preventing dementia or delaying cognitive decline in people with mild cognitive impairment. Cochrane Database Syst Rev. 2018 Nov 1;11(11):CD011905. Full text (https://www.doi.org/10.1002/14651858.CD011905.pub2) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/30383288?tool=bestpractice.bmj.com)

113. Laird EJ, O'Halloran AM, Molloy AM, et al. Low vitamin B(12) but not folate is associated with incident depressive symptoms in community-dwelling older adults: a 4-year longitudinal study. Br J Nutr. 2023 Jul 28;130(2):268-75. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/34895361?tool=bestpractice.bmj.com)

114. Niklewicz A, Smith AD, Smith A, et al. The importance of vitamin B(12) for individuals choosing plant-based diets. Eur J Nutr. 2023 Apr;62(3):1551-9. Full text (https://www.doi.org/10.1007/s00394-022-03025-4) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/36469110?tool=bestpractice.bmj.com)

115. Seal EC, Metz J, Flicker L, et al. A randomized, double-blind, placebo-controlled study of oral vitamin B12 supplementation in older patients with subnormal or borderline serum vitamin B12 concentrations. J Am Geriatr Soc. 2002 Jan;50(1):146-51. Abstract (http://www.ncbi.nlm.nih.gov/pubmed/12028259?tool=bestpractice.bmj.com)

Images

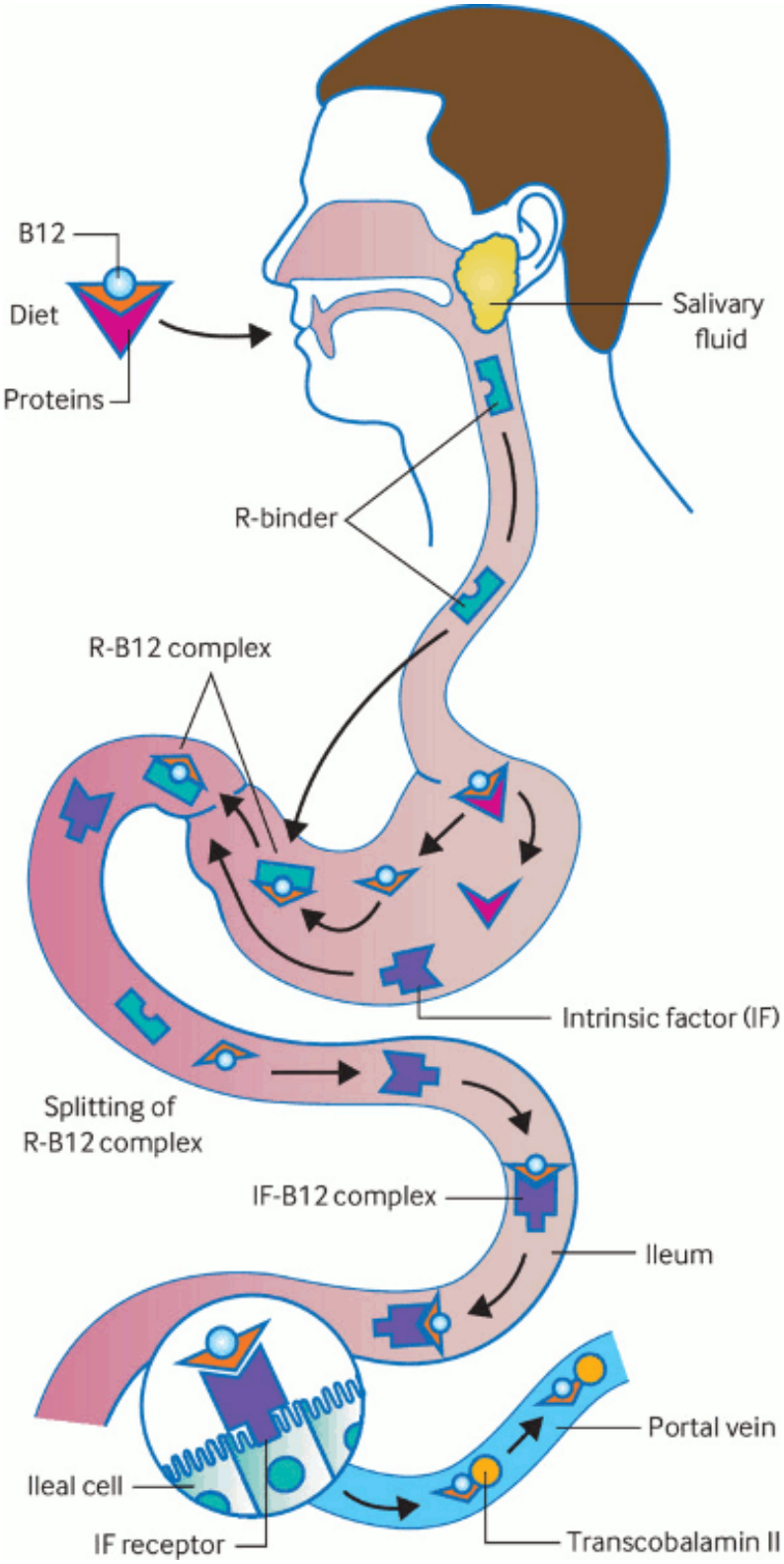


Figure 1: Absorption of vitamin B12. Dietary B12 is released from food in the stomach and binds to R-protein (haptocorrin, this complex is stable in the gastric acidic environment). The R-B12 complex then travels to the duodenum, where B12 binds to intrinsic factor (IF, secreted by gastric parietal cells and therefore lost in pernicious anemia). This B12-IF complex is carried down the small intestine until the terminal ileum, where it attaches to IF receptors and is absorbed into the bloodstream bound to transcobalamin. Over 95% of dietary B12 is absorbed through the IF pathway

Sukumar N et al. Investigating vitamin B12 deficiency. BMJ. 2019 May 10;365:l1865; used with permission

Disclaimer

BMJ Best Practice is intended for licensed medical professionals. BMJ Publishing Group Ltd (BMJ) does not advocate or endorse the use of any drug or therapy contained within this publication nor does it diagnose patients. As a medical professional you retain full responsibility for the care and treatment of your patients and you should use your own clinical judgement and expertise when using this product.

This content is not intended to cover all possible diagnosis methods, treatments, follow up, drugs and any contraindications or side effects. In addition, since such standards and practices in medicine change as new data become available, you should consult a variety of sources. We strongly recommend that you independently verify specified diagnosis, treatments and follow-up and ensure it is appropriate for your patient within your region. In addition, with respect to prescription medication, you are advised to check the product information sheet accompanying each drug to verify conditions of use and identify any changes in dosage schedule or contraindications, particularly if the drug to be administered is new, infrequently used, or has a narrow therapeutic range. You must always check that drugs referenced are licensed for the specified use and at the specified doses in your region.

Information included in BMJ Best Practice is provided on an “as is” basis without any representations, conditions or warranties that it is accurate and up to date. BMJ and its licensors and licensees assume no responsibility for any aspect of treatment administered to any patients with the aid of this information. To the fullest extent permitted by law, BMJ and its licensors and licensees shall not incur any liability, including without limitation, liability for damages, arising from the content. All conditions, warranties and other terms which might otherwise be implied by the law including, without limitation, the warranties of satisfactory quality, fitness for a particular purpose, use of reasonable care and skill and non-infringement of proprietary rights are excluded.

Where BMJ Best Practice has been translated into a language other than English, BMJ does not warrant the accuracy and reliability of the translations or the content provided by third parties (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages). BMJ is not responsible for any errors and omissions arising from translation and adaptation or otherwise.Where BMJ Best Practice lists drug names, it does so by recommended International Nonproprietary Names (rINNs) only. It is possible that certain drug formularies might refer to the same drugs using different names.

Please note that recommended formulations and doses may differ between drug databases drug names and brands, drug formularies, or locations. A local drug formulary should always be consulted for full prescribing information.

Treatment recommendations in BMJ Best Practice are specific to patient groups. Care is advised when selecting the integrated drug formulary as some treatment recommendations are for adults only, and external links to a paediatric formulary do not necessarily advocate use in children (and vice-versa). Always check that you have selected the correct drug formulary for your patient.

Where your version of BMJ Best Practice does not integrate with a local drug formulary, you should consult a local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing before prescribing.

Interpretation of numbers

Regardless of the language in which the content is displayed, numerals are displayed according to the original English-language numerical separator standard. For example 4 digit numbers shall not include a comma nor a decimal point; numbers of 5 or more digits shall include commas; and numbers stated to be less than 1 shall be depicted using decimal points. See Figure 1 below for an explanatory table.

BMJ accepts no responsibility for misinterpretation of numbers which comply with this stated numerical separator standard.

This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

Our full website and application terms and conditions can be found here: Website Terms and Conditions.

Contact us

+ 44 (0) 207 111 1105
support@bmj.com

BMJ
BMA House
Tavistock Square
London
WC1H 9JR
UK

Contributors:

// Authors:

Robert C. Oh, MD, MPH, CAQSM

Associate Chief of Staff, Education
VA Puget Sound Health Care System, Seattle, WA
DISCLOSURES: RCO declares that he has no competing interests.

// Peer Reviewers:

Thein Hlaing Oo, MD, FRCP Edin, FACP

Professor of Internal Medicine
Consultant Hematologist, The University of Texas MD Anderson Cancer Center, Houston, TX
DISCLOSURES: THO declares that he has no competing interests.

Rebecca Connor, MD

Chief Fellow
Section of Hematology and Oncology, Department of Internal Medicine, Wake Forest University Baptist Medical Center, Winston-Salem, NC
DISCLOSURES: RC declares that she has no competing interests.