# Review

# The role of Vitamin B12 in the critically ill—a review

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**Summary**

Vitamin B12 is an essential micronutrient, as humans have no capacity to produce the vitamin and it needs to be ingested from animal proteins. The ingested Vitamin B12 undergoes a complex process of absorption and assimilation. Vitamin B12 is essential for cellular function. Deficiency affects 15% of patients older than 65 and results in haematological and neurological disorders. Low levels of Vitamin B12 may also be an independent risk factor for coronary artery disease. High levels of Vitamin B12 are associated with inflammation and represent a poor outlook for critically ill patients. Treatment of Vitamin B12 deficiency is simple, but may be lifelong.

**Key Words:** vitamin B12, essential micronutrient, deficiency, excess, mortality

Vitamin B12, also known as cobalamin, is a water-soluble vitamin produced in nature by microorganisms. Humans cannot synthesise Vitamin B12 and are totally dependent on dietary sources. The recommended daily allowance of Vitamin B12 is 2.4 µg for men and non-pregnant women and 2.6 µg for pregnant women[1]. The main source of Vitamin B12 in a non-vegetarian Western diet is associated with the intake of animal proteins. Meat is the richest source of cobalamin containing over 10 µg/100 g wet weight. Fish, milk products and egg yolks contain 1 to 10 µg/100 g wet weight. As a result, the average non-vegetarian Western diet will contain 5 to 7 µg/day of Vitamin B12, which is sufficient to maintain normal cobalamin homeostasis. Most vegetarians only ingest 0.25 to 0.5 µg/day of cobalamin (molar mass 1355.37 g/mol) and are at risk for cobalamin deficiency[2]. Once body stores (mainly in the liver) of Vitamin B12 are saturated, it would take six to 12 months to become Vitamin B12 deficient if there was no further Vitamin B12 intake[3]. Both high and low levels of cobalamin in the body are associated with disease states, as discussed in this review.

## Absorption

Cobalamin is usually consumed in the form of a coenzyme deoxyadenosylcobalamin or methylcobalamin and is protein-bound. Proteolysis within the stomach (at low pH) is the first step in the release of Vitamin B12 from the food protein. Once released, the cobalamin binds to an R protein (released from salivary and gastric juice), which is a high-affinity cobalamin-binding protein (see Figure 1). The parietal cells of the stomach produce intrinsic factor (IF). The IF, together with the cobalamin–R protein complex, passes into the second part of the duodenum. Pancreatic proteases

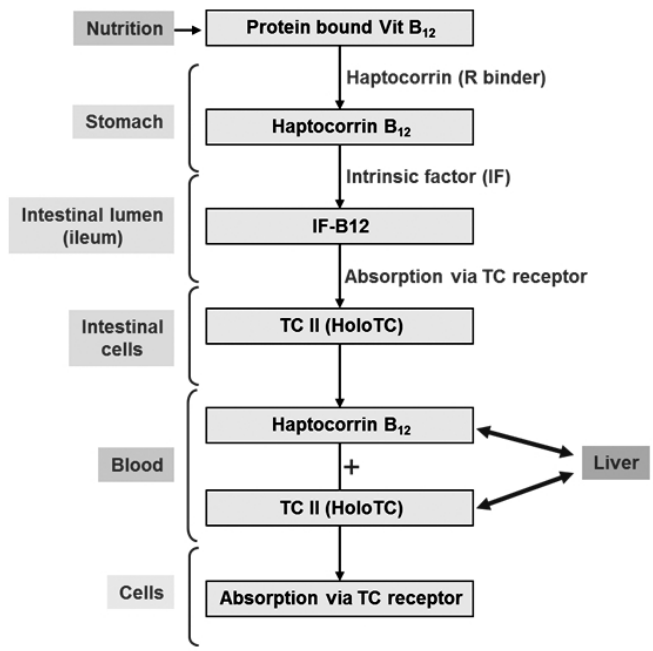


Figure 1: Transport and cellular absorption of Vitamin B12. (Adapted with kind permission from: Herrmann W, Obeid R. Causes and early diagnosis of Vitamin B12 deficiency[5].)
Key: TC, transcobalamin.

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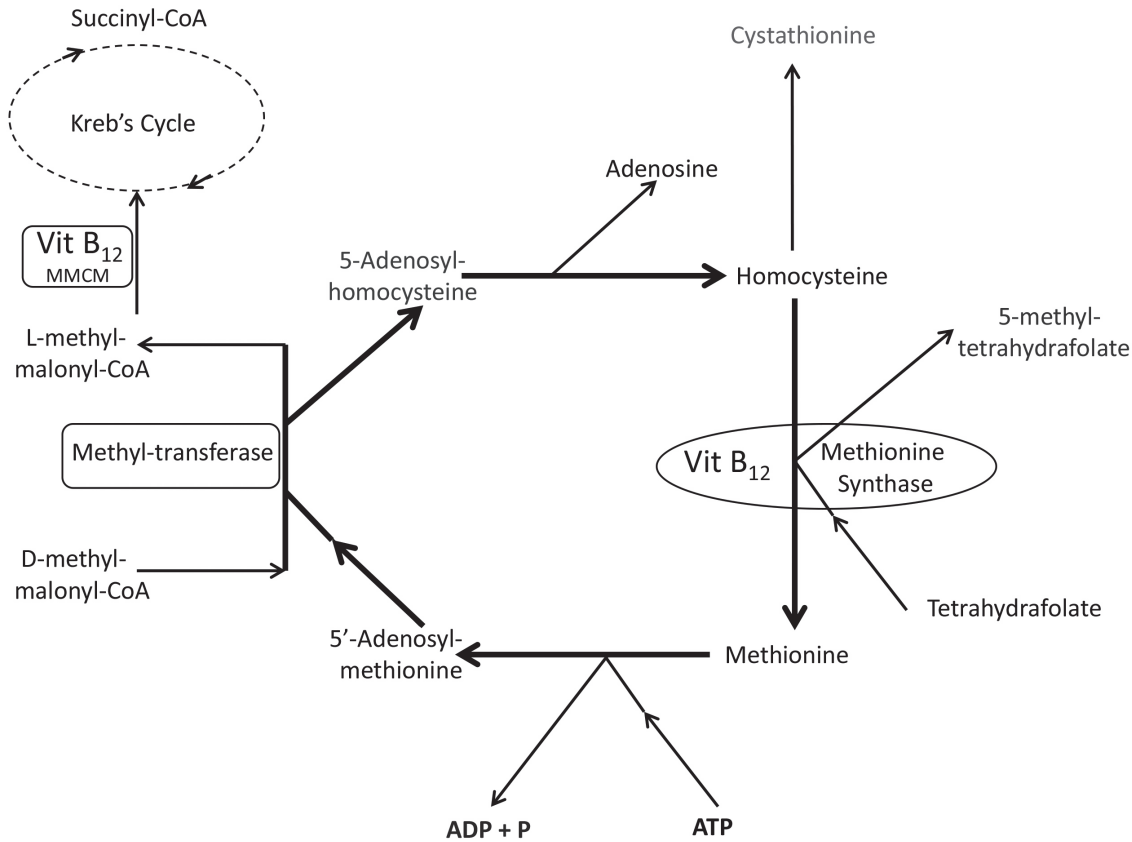


Figure 2: Vitamin B12 in energy metabolism[8]. Key: ATP, adenosine triphosphate; ADP, adenosine diphosphate; P, phosphate; MMCM, methylmalonyl–coenzyme A (CoA) mutase.

degrade the R proteins, thereby allowing the transfer of cobalamin to IF. The intrinsic factor–cobalamin complex then passes through the jejunum to the ileum, where it binds to membrane-associated intrinsic factor–cobalamin receptors located on the microvilli of ileal mucosal cells. The cobalamin enters the enterocyte and is transferred to transcobalamin II (holotranscobalamin), which binds to transcobalamin (TC) II receptors located on the cell surface. The cobalamin enters the circulation, mainly carried by TC II and to a lesser extent, TC I (haptocorrin). Cobalamin enters the cell via the TC receptor. Within the cell, cobalamin is bound to two intracellular enzymes, methylmalonyl–coenzyme A (CoA) mutase (MMCM) in mitochondria and methionine synthase (MeCbl) in the cytosol[4].

## Cellular metabolism

Vitamin B12 is involved in many key metabolic pathways involved in lipid, carbohydrate and protein metabolism. Vitamin B12 also plays a central role in haemopoiesis.

For protein synthesis, Vitamin B12 bound to MeCbl facilitates the removal of a methyl group from methylfolate to form homocysteine (HCYS), which is converted to methionine. This allows for the recycling of 5-methyl-tetrahydrofolate (5MeTHF) to N–510, methylene tetrahydrofolate, which is needed for the de novo synthesis of thymidylic acid, a precursor in DNA synthesis[6]. Vitamin B12 is also required for the isomerisation of d-leucine to leucine which is found in certain regulatory proteins like transcription factors NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells), Myc and Fos. Vitamin B12 may therefore have a secondary oncogene role[7].

Vitamin B12 is also essential for cellular respiration and energy by acting on the Krebs cycle at a critical stage. The Krebs cycle produces cellular energy in the form of adenosine triphosphate (ATP). Vitamin B12 bound to MMCM mediates the isomerisation of methylmalonyl CoA to succinyl CoA. Succinyl CoA is a critical point in the Krebs cycle where numerous intermediaries of metabolism enter and exit[6] (Figure 2).

## Measurement

There is currently no gold standard for the measurement of Vitamin B12. As described above, Vitamin B12 is transported by two main proteins, TC I (haptocorrin) and TC II (holoTC). HoloTC binds only a small fraction (20%–30%) of total plasma Vitamin B12, but is the main transporter of Vitamin B12 to

cells and therefore is the functionally important fraction. Haptocorrin binds the majority of Vitamin B12. This complex is inert, as haptocorrin does not deliver Vitamin B12 to the cells. Haptocorrin may reflect the general underlying state of Vitamin B12 stores[9].

In a patient with clinical and laboratory signs consistent with Vitamin B12 deficiency, measurement of total plasma Vitamin B12 levels using chemiluminescence is the usual first-line test. This test is better for assessing long-term rather than short-term deficiency as concentrations only decrease late in depletion. Frank Vitamin B12 deficiency (less than 148 pmol/l) will be detected with 90%–95% sensitivity and about 80% specificity. For subclinical deficiency (less than 220 pmol/l), sensitivity ranges between 40% and 80%[10,11]. HIV infection, folate deficiency and pregnancy may cause falsely low values.

In cases of suspected deficiency, but normal or borderline values of plasma Vitamin B12, holoTC or surrogate markers of Vitamin B12 deficiency may be tested. Surrogate markers include methylmalonic acid (MMA) and total HCYS. Vitamin B12 deficiency is associated with increased plasma concentrations of HCYS and MMA[9,12]. Total plasma Vitamin B12 levels, combined with either holoTC or MMA, provide improved positive predictive values for improved outcome. HoloTC levels reflect recent changes in Vitamin B12 status and fall sooner in negative Vitamin B12 balance. MMA can also be used to monitor response to treatment, as values return to normal seven to 10 days after Vitamin B12 stores are replete. All the tests may be falsely elevated with liver or renal disease[9].

## Vitamin B12 in disease

While the entity of megaloblastic anaemia is well recognised, along with the neurological effects of deficiency of Vitamin B12, other effects of deficiency of Vitamin B12 have also been investigated. High Vitamin B12 levels may also be a significant marker of ill-health[13].

## Deficiency

Vitamin B12 deficiency may result from many factors, including decreased intake and factors that interfere with the absorption of Vitamin B12 from the digestive tract (see Figure 1). Vitamin B12 levels may therefore be decreased in many of the patients admitted to the intensive care unit (ICU) such as patients with burns or severe trauma, elderly patients, those receiving chronic renal replacement therapy, and also following gastric surgery, in small bowel disorders and pancreatic insufficiency, and with the use of drugs like proton pump inhibitors, metformin and angiotensin converting enzyme inhibitors[6,14].

Rodriguez et al showed that 2% of patients admitted to the ICU were Vitamin B12 deficient and advised testing levels in all patients with a prolonged stay in the ICU[15]. The prevalence of Vitamin B12 deficiency is higher in patients over 65 years of age, up to 15%[16,17]. As the average age of patients admitted to ICU is increasing, we can expect to see more patients in the ICU with the deficiency.

Vitamin B12 deficiency causes reversible megaloblastic anaemia, demyelinating neurological disease, or both (see Table 1). As seen above, Vitamin B12 is a cofactor for the coenzymes MeCbl and MMCM. Without the cofactor (Vitamin B12), cells cannot mature correctly and megaloblastic anaemia occurs. Macrocytosis and hypersegmented nuclei are found in the peripheral blood smear. Within the bone marrow, the ineffective erythropoiesis causes intramedullary haemolysis. The above factors may cause anaemia, thrombocytopenia or even pancytopenia[18].

Vitamin B12 is also necessary for the development, initial myelination and ongoing maintenance of the central nervous system. Vitamin B12 deficiency may cause subacute combined degeneration (also known as combined systems disease) as a result of demyelination of the cervical and thoracic dorsal and lateral columns of the spinal cord and demyelination of the white matter of the brain. This may present clinically with altered mental status, cognitive defects, irritability, mania, depression, paraesthesiae, myelopathy and loss of proprioception. Demyelination of cranial and peripheral nerves may also occur, which may present clinically with optic atrophy, anosmia, paraesthesiae, incontinence and impotence[4,18] (See Table 1).

Nitrous oxide exposure appears to block the action of Vitamin B12 and may lead to a neuropathy very similar to combined degeneration. This may be of importance after prolonged anaesthesia or prolonged and heavy recreational

Table 1
*Vitamin B12 deficiency*

| Organ system | Vitamin B12 deficiency | Clinical presentation |
|---|---|---|
| Brain and nervous system | 1.Demyelination of cervical and thoracic dorsal + lateral columns of spinal cord (subacute combined degeneration)<br>2.Demyelination of white matter<br>3.Demyelination of cranial and peripheral nerves | 1.Myelopathy, parasthesiae, loss of proprioception<br>2.Altered mental status, cognitive defects, irritability, mania, depression<br>3.Optic atrophy, anosmia, glossitis, incontinence and impotence |
| Bone marrow | 1.Ineffective erythropoiesis | 1.Hypercellular erythroid precursors, dyssynchrony between maturation of nuclei and cytoplasm, intramedullary haemolysis |
| Peripheral blood | 1. Megaloblastic anaemia<br>2. Haemolysis | 1.Macrocytosis, hypersegmented neutrophils, leukopenia, thrombocytopenia and pancytopenia<br>2.Increased LDH, increased indirect bilirubin, decreased haptoglobin |

abuse[8]. Vitamin B12 deficiency may also result in elevated HCYS levels, which is an independent risk factor for coronary artery disease[19].

## Treatment of deficiency

The recommended daily requirement for Vitamin B12 is 2.4 µg/day[1]. Higher doses may be required during acute illness, although no formal guidelines exist. A Danish study showed that a daily dose of 6 µg caused a reversal of biochemical markers of Vitamin B12 deficiency[20]. Patients with proven Vitamin B12 deficiency can be supplemented orally or intramuscularly (IM), depending on cause and severity.

### *Oral treatment*

In patients with good enteral absorption, oral supplementation can be given with a daily tablet containing 1 mg of cobalamin. Following oral administration of this dose of Vitamin B12, only five to 40 µg of cobalamin is bioavailable[21].

### *Intramuscular injection*

For patients with problems with enteral absorption, IM Vitamin B12 should be used at a dose of 1 mg. IM injection of Vitamin B12 bypasses the digestive tract and therefore factors decreasing the absorption of Vitamin B12 (see above) can be bypassed.

A study compared patients who received either 1 mg oral or 1 mg IM Vitamin B12 daily, for a week, then weekly for four weeks and then monthly for life[22]. Haematological and recovery parameters were similar between the two groups. The benefit of oral treatment in terms of patient comfort and compliance should be considered. Another trial comparing different doses of oral Vitamin B12, showed the optimal dose of oral Vitamin B12 needed to effect an 80%–90% reduction in MMA was between 647 and 1032 µg daily[23].

### *Treatment regimens*

Initial treatment regimens and duration of treatment vary. One regimen suggests IM injections and starts with 8–10 injections over two months followed by monthly injections[24]. Other regimens include administering oral cobalamin daily for 10 days, then weekly for four weeks, followed by monthly administration[22]. The British National Formulary advises 1 mg IM Vitamin B12 three times a week for two weeks, then once every three months for patients with megaloblastic anaemia without neurological syndromes[25].

Haematologic abnormalities may reverse quickly and may lead to iron and folate deficiency due to consumption and it is advisable to co-administer iron and folate supplements[21-24]. The neurological symptoms may take longer to recover, depending on the duration of symptoms prior to commencing treatment[26]. Patients with poor diet or chronic malabsorption may require lifelong treatment to prevent relapse.

Routine monitoring of Vitamin B12 and haemoglobin levels should be performed every few months in patients receiving treatment for Vitamin B12 deficiency. MMA and HCYS levels may be better markers for detecting relapse earlier[24].

The American Society for Parenteral and Enteral Nutrition (ASPEN) guidelines[27] recommend 5 µg/day of Vitamin B12 to be included in parenteral nutrition. The dose is similar to the daily recommended oral dose despite the fact that only 50% of the Vitamin B12 administered orally is absorbed. It is speculated that 25% of parenteral Vitamin B12 is eliminated by the kidneys. Despite this, patients receiving chronic parenteral nutrition may have higher serum Vitamin B12 values (515–665 pmol/l).

High dose Vitamin B12 is generally safe, but there have been reports of allergy and anaphylactoid reactions to Vitamin B12[28].

## Vitamin B12 excess

High serum Vitamin B12 levels have been found in numerous conditions including renal failure, cancer, haematological malignancies (such as acute and chronic leukaemias), polycythaemia vera, hypereosinophilic syndrome, hepatic diseases (such as cirrhosis and hepatitis), and hepatocellular carcinomas[29-31]. In a recent study, elevated Vitamin B12 was found in patients with alcoholism, liver disease and cancer[32]. Numerous mechanisms cause high Vitamin B12 levels: elevated plasma levels of the carrier proteins TC I/III produced by myeloid, hepatic and other cell types, decreased Vitamin B12 clearance by the liver, decreased production of TC II by the liver and therefore decreased uptake by peripheral tissues, increased ingestion, or therapeutic administration[29,30,33].

Arendt et al proposed a diagnostic strategy for patients with high Vitamin B12[34]. Well-documented causes of excess should be excluded. These include hepatocellular carcinoma, autoimmune lymphoproliferative syndromes and chronic myeloid leukaemia. Other possible associations include other haematological diseases and cancers, and liver or renal disease. Infectious diseases, HIV/AIDS, and rheumatoid arthritis are debatable associations.

In a study by Corcoran et al in 2009 to investigate the relationship between vitamin levels and inflammation, a positive correlation was found between C-reactive protein (CRP) and elevated Vitamin B12 levels in the first two days of ICU admission[13]. The potential role of B12 status as an acute phase reactant needs further study.

In 2011 Sviri et al conducted a study to evaluate excess Vitamin B12 levels as an independent risk factor or marker for outcome in critically ill patients[35]. In that study of 663 patients admitted to the medical intensive care unit (MICU), non-survivors had a higher mean Vitamin B12 value than survivors (1270 pmol/l versus 740 pmol/l; $P$ <0.01). The patients who died by 90 days after admission to the MICU

also had higher mean Vitamin B12 levels than survivors (1175 pmol/l versus 730 pmol/l). The increased 90-day mortality with increased Vitamin B12 levels was independent of other variables. The study also showed that Vitamin B12 level above 665 pmol/l independently predicted a higher mortality (normal Vitamin B12 range 150–665 pmol/l).

The effects of high Vitamin B12 levels in patients receiving long-term parenteral nutrition were studied by Elkhatib et al[36]. No correlation was found between Vitamin B12 levels and intestinal failure or associated liver disease.

## Therapeutic uses for high dose Vitamin B12

There are limited opportunities to use Vitamin B12 as a therapeutic agent. There are a few case reports of high dose hydroxycobalamin being used to reverse the toxic effects of cyanide poisoning[37,38]. Hydroxycobalamin combines with cyanide to form cyanocobalamin, which is excreted in the urine[6]. Wheatley[7] has hypothesised that Vitamin B12 in high doses could also be used to treat sepsis/SIRS due to its multiple effects: Vitamin B12 regulates growth factor and may lead to preservation of normal function of macrophages and the coagulation system; it regulates NF-κB (a key activator of the pro- and anti-inflammatory pathways); and Vitamin B12 may potentiate anti-inflammatory effects. It also helps restore optimal bacteriostasis and phagocytosis. Vitamin B12 is also known to be an antioxidant[6]. Despite the above theoretical advantages of Vitamin B12 in sepsis, its role has not been proven and indeed is somewhat counterintuitive when seen in light of more recent findings that high serum levels of Vitamin B12 in critically ill patients are a poor prognostic sign[35].

## Conclusions

Vitamin B12 is an essential micronutrient. Low levels of Vitamin B12 are associated with recognised syndromes and may be a precipitating factor in cardiovascular disease. High levels are associated with poor outcomes in critically ill patients. While it is essential to maintain normal levels of Vitamin B12, there appears to be a minimal role for therapeutic uses of Vitamin B12 in the absence of deficiency.

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