

# Vitamin B<sub>12</sub> deficiency

## Recognizing subtle symptoms in older adults

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Vitamin B<sub>12</sub> deficiency is a common but under-recognized, yet easily treatable disorder in older adults. Although several causes exist, food-cobalamin malabsorption is now believed to be the most common etiology. Complications of vitamin B<sub>12</sub> deficiency are myriad, ranging from lethargy and weight loss to dementia. Causes of deficiency include failure to separate vitamin B<sub>12</sub> from food protein, inadequate ingestion, absorption, utilization, and storage as well as drug-food interactions leading to malabsorption and metabolic inactivation. The roles of B<sub>12</sub> deficiency, elevated homocysteine and elevated methylmalonic acid in various disease states are still evolving. Timely screening and replacement of vitamin B<sub>12</sub> will help prevent many complications.

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homocysteine • methylmalonic acid

Vitamin B<sub>12</sub> deficiency is common in the geriatric population—prevalence varies from 3 to 40%.<sup>1</sup> Up to 25% of hospitalized older adults from the inner city community or nursing homes either have clear or borderline B<sub>12</sub> deficiency.<sup>2,3</sup>

B<sub>12</sub> exerts its physiologic effect on two major enzymatic pathways: the conversion of homocysteine to methionine and the conversion of methylmalonyl coenzyme A (CoA) to succinyl-CoA. Dis-

ruption of either of these pathways from B<sub>12</sub> deficiency results in elevation of both serum methylmalonic acid (MMA) and homocysteine. Whereas elevated homocysteine is likely vasculotoxic and neurotoxic, elevated MMA may explain the neurologic manifestations of B<sub>12</sub> deficiency. (For details on the biochemical process, see page 33.)

The current U.S. recommended dietary allowance of B<sub>12</sub> is 2.4 µg/d; content of typical multivitamins range up

to 30 µg. The average, daily dietary intake of B<sub>12</sub> in the United States ranges from 5 to 30 µg of which, only 1 to 5 µg is absorbed.<sup>4</sup> Dietary sources rich in B<sub>12</sub> include meat, fish, eggs and dairy products. Because B<sub>12</sub> is not present in foods of plant origin, strict vegetarians or vegans are at risk of developing B<sub>12</sub> deficiency at some point during their lifetime. Despite the presence of sufficient B<sub>12</sub> in the average American diet, deficiency remains a risk because B<sub>12</sub> absorption entails a complex pathway involving several steps at different sites along the gastrointestinal tract (table 1).<sup>4,5</sup> A defect in only one of these steps, either physiologic or pathologic, may induce deficiency. Conversely, excess B<sub>12</sub> is excreted through the urine.

### Causes of deficiency

Because the daily requirement for B<sub>12</sub> is small and the body is able to adequately store it, clinical deficiency typically takes years to develop.

Deficiency may occur for several reasons, but certain disorders need emphasis in older adults (table 2). Whereas pernicious anemia (PA) was once considered the most common etiology of B<sub>12</sub> deficiency, newer studies identify food-B<sub>12</sub> malabsorption as the cause for up to one-half of deficiency states in late life.<sup>6,7,8</sup> PA appears the basis only in a minority of cases.

Food-B<sub>12</sub> malabsorption refers to the inability to absorb food-bound B<sub>12</sub> even though absorption of free B<sub>12</sub> remains intact. Atrophic gastritis, irre-

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spective of cause, also results in B<sub>12</sub> malabsorption. *Helicobacter pylori* is a recognized cause of chronic gastritis and recent studies suggest that the treatment of *H. pylori* infection will improve B<sub>12</sub> status in those with deficiency without the need for replacement B<sub>12</sub> therapy.<sup>9</sup>

Pernicious anemia remains a treatable cause of B<sub>12</sub> deficiency in older adults; one recent survey of apparently healthy adults over age 60 suggested that approximately 2% had undiagnosed PA, many with preclinical B<sub>12</sub> deficiency.<sup>8</sup> In contrast to food-B<sub>12</sub> malabsorption, PA results in defective absorption of both food-bound and free B<sub>12</sub>.

Malabsorption resulting from small intestinal bacterial overgrowth (SIBO) is an important, yet often unrecognized cause of B<sub>12</sub> deficiency in geriatric patients. Older adults are more likely to suffer from conditions that predispose them to SIBO including reduced intestinal motility and achlorhydria. The prevalence of SIBO ranges from 15 to 50% in the older population;<sup>10</sup> here, deficiency is caused by the uptake of B<sub>12</sub> by microorganisms in the small intestine. Diagnosis of SIBO is through breath tests or culture of small intestinal aspirate to demonstrate abnormal bacterial counts. Typically, SIBO patients respond well to a wide variety of antibiotic treatment for several days; courses may need to be repeated.

Drug interactions causing B<sub>12</sub> deficiency also deserve consideration in older adults, who typically are prescribed multiple medications. Metformin, antibiotics, colchicine, and anticonvulsants can all cause vitamin B<sub>12</sub> malabsorption. Deficiency has been observed after 3 months of metformin use.<sup>11</sup> Vitamin C, used to promote wound healing, may cause the conversion of some vitamin B<sub>12</sub> into a metabolically inactive analogue. This does not mean, however, that the 2 vitamins need to be taken at different times of the day to prevent this from happening. Nitric oxide and other nitrates may induce deficiency by oxidizing B<sub>12</sub>, particularly following anesthesia.

Acid-lowering agents assume rele-



Cobalamin (B<sub>12</sub>) is absorbed by pinocytosis through the microvilli of the small intestine.

Illustration for Geriatrics by Jay Le Vasseur

vance because they are commonly used and are available over-the-counter. The acid-lowering action of these agents predispose older adults to hypochlorhydria and SIBO, both known to cause B<sub>12</sub> deficiency.<sup>12</sup> Gastroesophageal reflux disease (GERD) is common in older adults, and treatment with proton pump in-

hibitors has been associated with decrease in serum B<sub>12</sub> levels.<sup>13</sup> The long-term implications of acid-lowering agents need further study.<sup>3</sup>

Miscellaneous causes of vitamin B<sub>12</sub> deficiency include gastric or intestinal resection, Crohn's disease, chronic pancreatitis, intestinal amyloidosis, and HIV

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infection. Crohn's disease is more common than earlier realized, and many individuals develop the disease after age 60. Of those that develop Crohn's disease, one-half to two-thirds become B<sub>12</sub> deficient. Dietary deficiency, though uncommon, may play a role in strict vegetarians or vegans. In one European study, approximately 78% of vegans were found to have B<sub>12</sub> deficiency.<sup>14</sup> Rare causes of deficiency include primary gastric lymphoma and multiple myeloma.

## Clinical features

Herbert describes B<sub>12</sub> deficiency in four stages; stage 1 and stage 2 are associated with biochemical defects only, with normal serum B<sub>12</sub> levels; stages 3 and 4 are characterized by metabolic and clinical manifestations.<sup>3,4</sup>

*continued*

**Table 1 Pathway for gastrointestinal absorption of cobalamin**

### Oral cavity and stomach

R protein is secreted by salivary glands and gastric mucosa.

### Stomach

Cobalamin (Cbl) is separated from food by acid and peptic activity.

Liberated Cbl binds to R protein (forming Cbl-R complex).

IF is secreted by parietal cells.

### Duodenum

Cbl-R complex digested by pancreatic enzymes/alkalinity, frees Cbl.

Free Cbl binds to intrinsic factor (IF) in alkaline medium.

Cbl-IF complex moves down to terminal ileum.

### Terminal ileum

Cbl-IF complex binds to specific receptors on mucosal brush border.

### Mucosal cells

Cbl-IF complex bound to receptor undergoes pinocytosis.

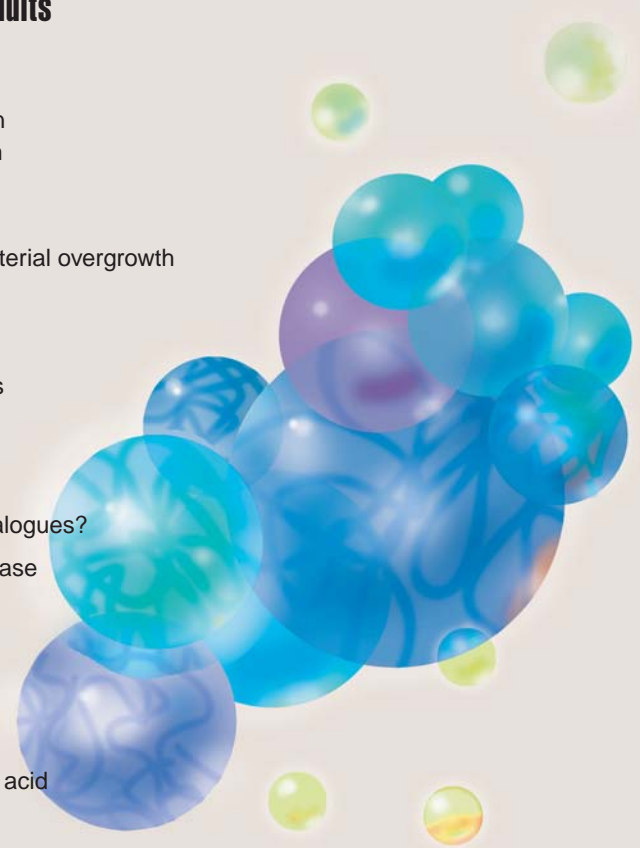
IF is degraded, Cbl transferred to TC-II and released into circulation (Holo transcobalamin).

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**Table 2 Causes of vitamin B<sub>12</sub> deficiency in older adults**

Mechanism	Causes
Inadequate ingestion	Chronic alcoholism Chronic malnutrition Strict vegetarianism
Inadequate absorption	Atrophic gastritis Gastrectomy Small intestinal bacterial overgrowth Intestinal resection Malabsorption Crohn's disease Chronic pancreatitis <i>H. pylori</i> gastritis
Inadequate utilization	Medications TC-II deficiency Anti-vitamin B <sub>12</sub> analogues?
Inadequate stores	Advanced liver disease
Drug interactions	
Malabsorption	Metformin Antibiotics Phenytoin Colchicine Para-aminosalicylic acid Cholestyramine
Metabolic inactivation	Vitamin C Nitrous oxide
Food-cobalamin malabsorption	Proton pump inhibitors H <sub>2</sub> receptor blockers

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## B<sub>12</sub>: Physiologic and metabolic actions

### Structure and physiologic actions of vitamin B<sub>12</sub>

Vitamin B<sub>12</sub> (cobalamin [Cbl]) consists of a porphyrin ring containing a central cobalt atom attached to a nucleotide. Whereas several analogues of cobalamin exist, only adenosylcobalamin and methylcobalamin have physiologic activity in humans.

In humans, B<sub>12</sub> exerts its physiologic effect on two major enzymatic pathways (table A). In the first, methylcobalamin is a cofactor in the conversion of homocysteine to methionine. This reaction is essential for the conversion of dietary and storage folate (methyltetrahydrofolate) to tetrahydrofolate. If this pathway is impaired, methyltetrahydrofolate accumulates along with an increase in serum homocysteine. It is presently recognized that homocysteine is both vasculotoxic and neurotoxic.<sup>3</sup> In the second enzymatic pathway, adenosylcobalamin is a cofactor in the conversion of methylmalonyl coenzyme A (CoA) to succinyl-CoA. Diminished activity in this pathway results in an increase in serum methylmalonic acid (MMA), a hydrolysis product of methylmalonyl-CoA. When this occurs, abnormal fatty acid synthesis involving the neuronal membranes may provide a possible explanation for neurologic manifestations that occur in B<sub>12</sub> deficiency. Thus, B<sub>12</sub> deficiency results in elevation of both MMA and homocysteine in the blood.

### Absorption, storage, and excretion

The initial step in absorption involves the release of Cbl from food proteins with the help of acid and pepsin. After cobalamin is released, it binds with R protein that is primarily produced by the salivary glands. As R-protein has a high binding affinity for Cbl at acid pH, most dietary Cbl becomes bound to R-protein (and not intrinsic factor) in the stomach. In the duodenum, pancreatic proteases along with bicarbonate hydrolyse the R-protein to again release vitamin B<sub>12</sub>, which then binds with intrinsic factor (IF) secreted by gastric parietal cells. The Cbl-IF complex

is able to resist proteolytic digestion and travels to the terminal ileum where it binds to specific receptors on the brush border of the mucosal cells before it is internalized by pinocytosis. This process requires the participation of free calcium. Intracellular cobalamin is released from the Cbl-IF complex and IF is degraded. Free B<sub>12</sub> next attaches to transcobalamin-II (TC-II), another carrier protein, and is released into the blood stream. Cobalamin attached to TC-II is referred to as holo TC-II and is taken up

**Table A Cobalamin-dependent biochemical pathways**

	Pathway one	Pathway two
Reaction	Hcy to methionine	Methylmalonyl CoA to succinyl CoA
Enzyme	Methionine synthase	Methylmalonyl CoA mutase
Co-enzyme	Methylcobalamin	Adenosylcobalamin
Result	Increased Hcy	Increased MMA

MMA: methylmalonyl acid Hcy: homocysteine

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by liver, bone marrow, and other cells. Besides TC-II, vitamin B<sub>12</sub> also may be bound to TC-I and TC-III in human serum. Both forms are referred to as haptocorrins and they are believed to serve mainly a storage function. An alternative route of absorption, passive diffusion throughout the entire length of the small intestine, has been suggested when vitamin B<sub>12</sub> is consumed in large amounts.<sup>4</sup>

The liver contains 50 to 90% of the body stores of cobalamin and the average adult stores from 3 to 5 mg of Cbl. Small amounts of Cbl are excreted daily in the bile and almost completely reabsorbed in the ileum. This efficient enterohepatic circulation may be useful in the elimination of noncobalamin B<sub>12</sub> analogues because cobalamin appears to be preferentially reabsorbed.<sup>4</sup> This enterohepatic circulation is especially important for B<sub>12</sub> homeostasis in vegetarians. Normally, only trace amounts of the vitamin appear in urine or stools. However, a significant amount of Cbl is excreted in urine when B<sub>12</sub> is given parenterally.

Vitamin B<sub>12</sub> deficiency may be asymptomatic or manifest with myriad neurologic or hematologic features or both.<sup>3</sup> Day-to-day complaints, such as lethargy or weakness, contrast with life-threatening manifestations, such as leukopenia or thrombocytopenia.<sup>15</sup> A secondary effect

of B<sub>12</sub> deficiency occurs on the entire proliferating gastrointestinal epithelium, with resultant anorexia, glossitis, weight loss, and malabsorption.

The major and obvious hematologic abnormality of B<sub>12</sub> deficiency is anemia with classic macro-ovalocytosis,

although anemia need not be present. Other laboratory features are detailed in table 3.

Neuronal damage begins with demyelination and axonal degeneration eventually resulting in neuronal death.<sup>16</sup> Manifestations vary depending on the

**Table 3 Laboratory features of cobalamin deficiency**

<b>Hematologic tests</b>	Anemia Thrombocytopenia Elevated mean corpuscular volume Leukopenia Low or normal reticulocyte count
<b>Peripheral smear</b>	Macroovalocytosis Hypersegmented neutrophils Anisocytosis Poikilocytosis
<b>Bone marrow</b>	Hypercellular Increased myeloid/erythroid ratio Abundant stainable iron Nuclear-cytoplasmic asynchrony Decreased megakaryocytes with abnormal morphology
<b>Chemistry</b>	Decreased serum vitamin B <sub>12</sub> Increased MMA Increased homocysteine Decreased Holo TC-II Increased unconjugated bilirubin Increased LDH (Isoenzyme 1)

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**Table 4 Conditions causing misleading vitamin B<sub>12</sub> levels**

**False positive (false low serum B<sub>12</sub> measurement) occurs in:**

- Folate deficiency
- Progressive multiple myeloma
- Use of oral contraceptive pills
- Multiple myeloma
- Excessive vitamin C intake

**False negative (false normal serum B<sub>12</sub> measurement) occurs in:**

- Active liver disease
- Lymphoma
- Alcoholism
- Intestinal bacterial overgrowth
- Myeloproliferative disorders

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involvement of peripheral nerves and the spinal cord, cerebrum, or both. Clinical features include subacute combined degeneration (ataxia, altered tendon reflexes, Romberg's sign and extensor plantar reflex) with or without paresthesia from peripheral neuropathy. Sphincter disturbances involving the bladder and cranial nerve palsies are known to occur. Mentation ranges from mild irritability to dementia, depres-

sion, and psychosis.<sup>17</sup> A dramatic acute demyelination with paraparesis has been reported following nitrous oxide anesthesia.<sup>18</sup> B<sub>12</sub> deficiency has been associated with dementias, particularly Alzheimer's dementia, and depression.<sup>19</sup>

### Screening and diagnosis

Screening for vitamin B<sub>12</sub> status in older adults is worthwhile because the prevalence of deficiency is high (up to 40%)

and the window of opportunity for treatment and reversal of neurologic complications is short, usually measured in months. Treatment is inexpensive and generally free of side effects.

A serum B<sub>12</sub> measurement is a reasonable initial screening test. The value may be limited as serum levels between 100 to 400 pg/mL do not reflect tissue status. False negative and false positive results may cloud the values (table 4). Serum B<sub>12</sub> levels below 100 pg/mL suggest deficiency, but discriminate poorly between 100 to 400 pg/mL. It is in this range that additional tests including serum homocysteine, serum MMA, and serum Holo TC-II assays should be considered.

Low serum Holo TC-II may be the earliest marker of vitamin B<sub>12</sub> deficiency,<sup>4</sup> however, assays are not widely available at present. Elevated serum MMA levels are fairly specific for vitamin B<sub>12</sub> deficiency and are a measure of tissue vitamin activity.<sup>20</sup> Still, levels of MMA may be elevated in chronic renal insufficiency and hypovolemia in the absence of B<sub>12</sub> deficiency. Although serum homocysteine is also a sensitive indicator of B<sub>12</sub> status, it too is elevated in several other states besides being an independent risk factor for atherosclerotic disease (see [www.geri.com/B12](http://www.geri.com/B12) for table B, which details causes of elevated MMA and homocysteine).<sup>21</sup>

There is no accepted screening protocol for vitamin B<sub>12</sub> deficiency; suggestions vary from screening every adult to simply treating every adult.<sup>8,20</sup> Individuals with risk factors predisposing to B<sub>12</sub> deficiency (table 2) should be screened at the first opportunity (table 5).<sup>4,20,22,23</sup>

Hematologic tests such as red blood cell, white blood cell, and platelet counts; mean corpuscular volume, hematocrit, and hypersegmented neutrophils lack sensitivity and may not necessarily be abnormal in early stages of B<sub>12</sub> deficiency. Hence, they are not reliable for diagnosis of deficiency if used alone.

Once B<sub>12</sub> deficiency is identified (defined as B<sub>12</sub> < 400 pg/mL), additional evaluations include anti-IF antibody-

ies, Schilling's test, thyroid function, and tests for malabsorption.<sup>24</sup>

Schilling's test involves administration of radiolabeled vitamin B<sub>12</sub> without Intrinsic Factor (IF), with IF, and following a course of antibiotics with measurement of urinary excretion of radiolabeled vitamin B<sub>12</sub>. The test helps identify pernicious anemia (absorption improves with IF), bacterial overgrowth (absorption improves with antibiotics) or pathologic conditions of the small bowel (all 3 stages abnormal), and is normal in food B<sub>12</sub> malabsorption. The need for 24-hour urine collections and presence of comorbidity such as dementia and renal insufficiency in older patients makes this a cumbersome test in older adults.

### Prophylaxis and treatment

To prevent deficiency, we recommend all patients over age 50 pay attention to B<sub>12</sub> intake, typically by encouraging patients to eat fortified foods (eg, fortified cereals, dairy products, fish), take supplements, or both. We encourage supplements because of the FDA decision to fortify cereals with folic acid as well as B<sub>12</sub>, which may mask or accelerate neurologic features in untreated B<sub>12</sub> deficiency.

Several treatment options are available. Commercial preparations are available for oral, IM, intranasal or sublingual administration (table 6). Traditional treatment involves intramuscular administration of vitamin B<sub>12</sub> (100 to 1,000 µg) daily for 3 to 7 days followed by monthly or quarterly injections. Clinical response to replacement is usually rapid with reticulocytosis observed in 2 to 5 days; the hematocrit normalizes over weeks. Neurologic symptoms may recover completely with timely treatment. Once initiated, B<sub>12</sub> replacement should continue for life. Specific therapy should be directed at treatable etiologies when applicable (eg, bacterial overgrowth).

Hypokalemia and fluid overload may occur early in treatment of megaloblastic anemia as a result of increased erythropoiesis, cellular uptake of potassium, and increase in blood volume.

**Table 5 Suggested screening for B<sub>12</sub> deficiency\***

Patient types	Recommendations
1. At risk, based on history, or presence of conditions that predispose deficiency (table 2)	Screen at first opportunity (irrespective of age)
2. All others, up to age 65	Initial screen at age 50, thereafter <ul style="list-style-type: none"> <li>• if serum B<sub>12</sub> &gt; 400 pg/mL, screen every 5 years</li> <li>• if serum B<sub>12</sub> 100 to 400 pg/mL, consider MMA and Hcy assays to confirm B<sub>12</sub> status</li> <li>• if serum B<sub>12</sub> &lt; 100 pg/mL, treat for deficiency</li> </ul>
3. All patients ≥ age 65	Screen annually
4. When deficiency confirmed	Test to elucidate etiology

MMA: methylmalmonic acid

Hcy: homocysteine

\*To date, there is no accepted screening protocol for vitamin B<sub>12</sub> deficiency.

Approaches vary considerably and testing may be individualized by the provider based on cost and availability.

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**Table 6 Therapeutic options to treat B<sub>12</sub> deficiency**

B <sub>12</sub> preparation	Geriatric maintenance dose
Intramuscular injection	100 to 1,000 µg every 1 to 3 months
Oral dosing	500 to 2,000 µg/d
Sublingual forms	2,000 µg/d
Intranasal administration	500 µg weekly

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### Other therapy modalities

When administered in sufficiently large doses, oral B<sub>12</sub> is effective, even in treating PA.<sup>25</sup> At doses of 500 to 2,000 µg/d, about 1% is absorbed by passive diffusion along the entire small intestine. Oral B<sub>12</sub> preparations are not well regulated by the FDA and have varied bioavailability. Compliance in the cognitively impaired remains an issue; surveillance with annual B<sub>12</sub> screening is recommended for all patients.

Vitamin B<sub>12</sub> is also available as an intranasal gel and as sublingual preparations. Both forms appear to offer distinct advantages for specific patient groups, such as the homebound, and those with cognitive impairment or

dysphagia. Large-scale studies are still needed to establish their overall effectiveness.

### Conclusion

The insidious nature and myriad manifestations of vitamin B<sub>12</sub> deficiency make its diagnosis challenging for even seasoned primary care physicians. Annual screening of all adults over age 65 will allow the tracking of seemingly minor declines in B<sub>12</sub> status and thereby provide annual opportunities for prevention, as well as early options for therapy. The full extent of B<sub>12</sub> deficiency may never be known; we should concentrate, rather, on prevention and treatment if possible. ☐

*continued*

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