THE JOURNAL OF FAMILY PRACTICE

B_{12} deficiency: A look beyond pernicious anemia

Food-B_{12} malabsorption—not pernicious anemia—is the leading cause of B_{12} malabsorption. It's also very subtle

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Practice recommendations

- Mild, preclinical B_{12} deficiency is associated with food-B_{12} malabsorption more often than with pernicious anemia. (**C**)
- The classic treatment for B_{12} deficiency—particularly when the cause is not a dietary deficiency—is 100 to 1000 mcg per month of cyanocobalamin, IM. (**B**)
- Oral crystalline cyanocobalamin is an effective treatment for food-B_{12} malabsorption, though it's effectiveness in the long term has not been demonstrated. (**B**)

If an image of an elderly patient with pernicious anemia is the first thing that comes to mind when you think of B_{12} deficiency, take note: That image could obfuscate a more common case of B_{12} deficiency—one caused by food-B_{12} malabsorption.

Food-B_{12} malabsorption, characterized by the inability to release B_{12} from food or its binding proteins, is actually the leading cause of B_{12} malabsorption, especially in elderly patients.[1–4] And unlike pernicious anemia, it's more likely to be associated with mild, preclinical B_{12} deficiency.[1,5]

Spotting this form of B_{12} deficiency requires that you focus on its nuances, such as its link to *Helicobacter pylori* infection and long-term antacid and biguanide use. It also requires that you consider not only a patient's serum B_{12} levels, but his homocysteine and methylmalonic acid levels, since they are considered more sensitive indicators of cobalamin deficiency.[6] Keying in on these indicators early will ensure prompt treatment, which typically includes intramuscular injections of the vitamin, but which could revolve around a more convenient option: oral B_{12}.

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A common problem that comes in many shades

B_{12} deficiency is common in elderly patients[7] and its incidence increases with age.[7,8] The Framingham study revealed a prevalence of 12% among elderly people living in the community.[8] Other studies focusing on those who are in institutions or who are sick and malnourished, have suggested a higher prevalence of 30% to 40%.[3,9]

The clinical manifestations of B_{12} deficiency are highly polymorphic and of varying severity ranging from milder conditions such as the common sensory neuropathy and isolated anomalies of macrocytosis and hypersegmentation of neutrophils, to severe disorders, including combined sclerosis of the

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TABLE 1

Clinical features of B_{12} deficiency[1,5,6,10–13]

HEMATOLOGIC	NEUROPSYCHIATRIC
Frequent*	**Classic**
Macrocytosis	Combined sclerosis of the spinal cord
Hypersegmentation of the neutrophils	**Frequent***
Aregenerative macrocytary anemia	Polyneurites (especially sensitive ones)
Medullary megaloblastosis ("blue spinal cord")	Ataxia
Rare	Babinski's phenomenon
Isolated thrombocytopenia and neutropenia	**Rare**
Pancytopenia	Cerebellar syndromes affecting the cranial nerves including optic neuritis, optic atrophy, urinary or fecal incontinence
Hemolytic anemia	**Possible**
Thrombotic microangiopathy (presence of schistocytes)	Cognitive impairment
DIGESTIVE	Stroke and atherosclerosis (hyperhomocysteinemia)
Classic	Parkinsonian syndromes
Hunter's glossitis	Multiple sclerosis
Jaundice	**OTHER**
LDH and bilirubin elevation	**Possible**
Rare	Atrophy of the vaginal mucosa
Resistant and recurring mucocutaneous ulcers	Chronic vaginal and urinary infections (especially mycosis)
	Hypofertility and repeated miscarriages
	Venous thromboembolic disease
	Angina (hyperhomocysteinemia)

* Reported in practice and recent literature.

spinal cord, hemolytic anemia and even pancytopenia (**TABLE 1**).[1,5,6,10–13]

B_{12} deficiency is often unrecognized or not investigated because the clinical manifestations can be very subtle. In fact, one of its manifestations—mild memory loss—can mimic the early stages of dementia.[14]

Further muddying the waters is the fact that B_{12} deficiency appears to be more common among patients who have a variety of chronic neurologic conditions such as stroke, Parkinson's disease, dementia, Alzheimer's disease, and depression—although it is unclear if these are causal relationships.[1,15] In our own studies in which we administered B_{12} to patients with dementia, we did not observe any improvement.[2,5] Other studies have had similar results.[16,17]

B_{12} deficiency is typically defined in terms of the serum concentration of B_{12}, as well as the concentration of homocysteine and methyl malonic acid—2 components of the cobalamin metabolic pathway. A deficiency exists if the patient's blood work reveals the following:[2,18]

- Serum B_{12} levels <150 pmol/L and either total serum homocysteine levels >13 µmol/L or methylmalonic acid levels >0.4 µmol/L (in the absence of renal failure and folate and vitamin B_6 deficiencies).
- Low serum holotranscobalamin levels <35 pmol/L.

The "classic" cause is not the most common

The principal causes of B_{12} deficiency include pernicious anemia, dietary deficiency, postsurgical malabsorption, and food-B_{12} malabsorption. Of note is the fact that there is typically a 5- to 10-year delay between the onset of B_{12} deficiency and the development of clinical

illness, in part because of hepatic stores of cobalamin (>1.5 mg).[1,19]

In elderly patients, B_{12} deficiency is classically caused by pernicious anemia,[3,7] the principal characteristics of which have been reported in detail in several reviews.[20–22] The one thing, of course, that bears repeating is that this form of anemia is associated with a lack of intrinsic factor, which facilitates the absorption of B_{12}.

B_{12} deficiency caused by dietary deficiency is more rare. Dietary causes of deficiency are limited to elderly people who are already malnourished, such as those living in institutions (they may consume inadequate amounts of foods containing vitamin B_{12}) and strict vegetarians.[1,19] (A typical Western diet contributes 3–30 mcg of B_{12} per day towards the recommended dietary allowance set by the Food and Nutrition Board of the Institute of Medicine (US) of 2.4 mcg/day for adults and 2.6 to 2.8 mcg/day during pregnancy.[23])

Over the past 20 years, postsurgical malabsorption of B_{12} has been on the decline, due in large part to the decreasing frequency of gastrectomy and surgical resection of the terminal small intestine.[1,2,5] There are, however, several disorders commonly seen in gastroenterology practice that may be associated with cobalamin malabsorption. These include deficiency in the exocrine function of the pancreas after chronic pancreatitis (usually alcoholic), lymphomas or tuberculosis (of the intestine), Crohn's disease, Whipple's disease, and occasionally celiac disease.[3,13]

Rounding out the list of causes of B_{12} deficiency is food-B_{12} malabsorption, which is the leading cause of B_{12} malabsorption—especially in elderly patients.[1–4] In our own studies in which we have followed more than 300 patients with a documented B_{12} deficiency, food-B_{12} malabsorption accounts for about 60% to 70% of the cases of B_{12} deficiency in elderly patients, whereas pernicious anemia accounts for only 15% to 25%.[5,24] In our study of 172 hospitalized patients with B_{12} deficiency (median age, 70), 53% had food-B_{12} malabsorption.[5]

A form of malabsorption that's tough to spot

Food-B_{12} malabsorption is a syndrome characterized by the inability to release B_{12} from food or intestinal transport proteins, particularly in the presence of hypochlorhydria, in which the absorption of "unbound" B_{12} is normal. As various studies have shown,[4,5,24] this syndrome is defined by B_{12} deficiency in the presence of sufficient food-B_{12} intake and normal Schilling test results, which rules out pernicious anemia. In theory, indisputable evidence of food-B_{12} malabsorption comes from using a modified Schilling test, which uses radioactive B_{12} bound to animal proteins (eg, salmon, trout) and reveals malabsorption when the results of a standard Schilling test are normal.[1,5,24]

Some authors have speculated about the significance of B_{12} deficiency related to food-cobalamin malabsorption,[1] because many patients have only mild clinical or hematological features. Several of our patients, however, have had significant features classically associated with pernicious anemia, including polyneuropathy, confusion, dementia, medullar-combined sclerosis, anemia, and pancytopenia.[5] Nevertheless, the partial nature of this form of malabsorption might produce a more slowly progressive depletion of B_{12} than does the more complete malabsorption engendered by disruption of intrinsic factor–mediated absorption. The slower progression of depletion probably explains why mild, preclinical deficiency is associated with food-B_{12} malabsorption more often than with pernicious anemia.[1,5]

H pylori, antacid use should raise suspicions

Food-B_{12} malabsorption is caused primarily by atrophic gastritis.[5] More than 40% of patients older than 80 years have gastric atrophy that might (or might not) be related to *H pylori* infection.[3,25] Other factors that contribute to

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Food-B_{12} malabsorption accounts for 60%–70% of the cases of B_{12} deficiency in elderly patients

TABLE 2

French hospital findings support use of oral B_{12} treatment[38–41,45]

STUDY CHARACTERISTICS (NUMBER OF PATIENTS)	THERAPEUTIC MODALITIES	RESULTS
Open prospective study of well-documented vitamin B_{12} deficiency related to food-B_{12} malabsorption (n=10)[39]	Oral crystalline cyanocobalamin: 650 mcg per day, for at least 3 months	• Normalization of serum vitamin B_{12} levels in 80% of the patients • Significant increase of hemoglobin (Hb) levels (mean of 1.9 g/dL) and decrease of mean erythrocyte cell volume (ECV) (mean of 7.8 fL) • Improvement of clinical abnormalities in 20% of the patients • No adverse effects
Open prospective study of low vitamin B_{12} levels not related to pernicious anemia (n=20)[40]	Oral crystalline cyanocobalamin: between 1000 mcg per day for at least 1 week	• Normalization of serum vitamin B_{12} levels in 85% of the patients • No adverse effects
Open prospective study of well-documented vitamin B_{12} deficiency related to food-B_{12} malabsorption (n=30)[38]	Oral crystalline cyanocobalamin: between 250 and 1000 mcg per day, for 1 month	• Normalization of serum vitamin B_{12} levels in 87% of the patients • Significant increase of Hb levels (mean of 0.6 g/dL) and decrease of ECV (mean of 3 fL); normalization of Hb levels and ECV in 54% and 100% of the patients, respectively • Therapeutic dose of vitamin B_{12} ≥500 mcg per day • No adverse effects
Open prospective study of low vitamin B_{12} levels not related to pernicious anemia (n=30)[41]	Oral crystalline cyanocobalamin: between 125 and 1000 mcg per day for at least 1 week	• Normalization of serum vitamin B_{12} levels in all patients with at least a dose of vitamin ≥250 mcg per day • Therapeutic dose of vitamin B_{12} ≥500 mcg per day • No adverse effects
Open prospective study of low vitamin B_{12} levels related to pernicious anemia (n=10)[45]	Oral crystalline cyanocobalamin: 1000 mcg per day, for at least 3 months	• Significant increase of serum vitamin B_{12} levels in 90% of the patients (mean of 117.4 pg/mL) • Significant increase of Hb levels (mean of 2.45 g/dL) and decrease of ECV (mean of 10.4 fL) • Improvement of clinical abnormalities in 30% of the patients

food-B_{12} malabsorption in elderly people include:

- Chronic carriage of *H pylori* and intestinal microbial proliferation (in which case B_{12} deficiency can be corrected by antibiotic treatment)[25,26]
- Long-term ingestion of antacids, including H_2-receptor antagonists and proton-pump inhibitors,[27,28] particularly among patients with Zollinger-Ellison syndrome[29,30]
- Long-term ingestion of biguanides (metformin)[31–33]
- Chronic alcoholism
- Surgery or gastric reconstruction (eg, bypass surgery for obesity)
- Partial pancreatic exocrine failure[1,5]
- Sjögren's syndrome or systemic sclerosis[34]

In our research involving 92 elderly patients (mean age: 76 years) with food-B_{12} malabsorption,[5] we found at least one of the associated conditions or agents listed at left in 60% of the patients. These conditions mainly included atrophic gastritis (*H pylori* infection) in 30% of the patients and long-term metformin or antacid intake in 20% of the elderly patients.

IM injection is customary, though dosages vary

The classic treatment for B_{12} deficiency, particularly when the cause is not a dietary deficiency, is parenteral administration—usually by intramuscular injection—of cyanocobalamin (and in rare occasions, hydroxocobalamin).[7,11,16,35] In the US and UK, dosages range from 100 to 1000 mcg per month (or every 2–3 months when hydroxocobalamin is

given). The patient will receive this treatment for the rest of his life.[1,35]

In France, the recommended practice is to build up the tissue stores of the vitamin quickly and correct serum B_{12} hypovitaminosis, particularly in the case of pernicious anemia. The treatment involves administering 1000 mcg of cyanocobalamin per day for 1 week, followed by 1000 mcg per week for 1 month, followed by 1000 mcg per month, normally for the rest of the patient's life.[2,3,20]

Oral therapy is a well-kept secret

In cases of B_{12} deficiency that don't involve nutritional deficiency, alternative routes of cobalamin administration, including the oral[16,35–42] and nasal[43,44] routes have been used. These alternative routes offer patients a way to avoid the discomfort, inconvenience, and cost of an office visit for monthly injections.

Our research team has developed an effective oral treatment of food-B_{12} malabsorption[38–41] and for pernicious anemia[45] using crystalline cobalamin (cyanocobalamin). Our principal studies of oral B_{12} treatment (open, not randomized studies) are described in **TABLE 2**.[38–41,45] Our data confirm the previously reported efficacy of oral crystalline cyanocobalamin, especially in food-B_{12} therapy.[6,16,36] All of our patients who received oral therapy corrected their B_{12} levels and at least two thirds corrected their hematological abnormalities.[38–41,45] Moreover, one third of patients experienced a clinical improvement on oral treatment. In most cases of food-B_{12} malabsorption, a "low" B_{12} dose (ie, 125–1000 mcg of oral crystalline cyanocobalamin per day) was used.

These data are in line with the results of the 2 prospective randomized controlled studies comparing oral B_{12} with intramuscular B_{12} therapy.[35,37] An evidence-based analysis by the Vitamin B_{12} Cochrane Group supports the efficacy of oral B_{12} therapy, with doses between 1000 and 2000 mcg given daily in the beginning, and then weekly.[46] In this analysis, serum B_{12} levels increased significantly in patients receiving oral vitamin B_{12} and both groups of patients (receiving oral and intramuscular treatment) had neurological improvement.

In a randomized, parallel-group, double-blind, dose-finding trial, Eussen et al showed that the lowest dose of oral cyanocobalamin required to normalize mild B_{12} deficiency is more than 200 times the recommended dietary allowance of approximately 3 mcg daily (ie, >500 mcg/day).[47] The procedure for oral B_{12} treatment has, however, not been completely validated yet in "real life," particularly as it relates to long-term efficacy.[48] Nonetheless, several authors suggest that oral B_{12} therapy remains one of medicine's "best-kept secrets."[49] ■

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Acknowledgements

We are indebted to Professor Marc Imler and Jean-Louis Schlienger who initiated this work and to Helen Fothergill who kindly edited the text for publication in this English-language journal.

Disclosure

Emmanuel Andrès reports that his research on B_{12} deficiency was supported by a grant from the Fondation de France (Prix Robert et Jacqueline Zittoun 2004).

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All patients treated with oral therapy corrected their B_{12} levels and at least two thirds corrected their hematological abnormalities

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Oral B_{12} therapy has not been completely validated in "real life," though several authors call it one of medicine's best-kept secrets

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