B12 Deficiency

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Vitamin B12 (cobalamin) is a water-soluble vitamin that is crucial to normal neurologic function, red blood cell production, and DNA synthesis.

Vitamin B12 is essential for three enzymatic processes:

1. The conversion of homocysteine to methionine
2. The conversion of methylmalonic acid to succinyl coenzymeA
3. The conversion of 5-methyltetrahydrofolate to tetrahydrofolate, a process necessary for DNA synthesis and red blood cell production.
Vitamin B12 cannot be manufactured by humans and must be regularly obtained from the ingestion of animal proteins or fortified cereal products.

Gastric acid liberates vitamin B12 from animal proteins, after which it combines with intrinsic factor produced by gastric parietal cells and is absorbed in the terminal ileum.
Risk Factors for Vitamin B12 Deficiency

**Decreased ileal absorption**
- Crohn disease
- Ileal resection
- Tapeworm infestation

**Decreased intrinsic factor**
- Atrophic gastritis
- Pernicious anemia
- Postgastrectomy syndrome (includes Roux-en-Y gastric bypass)

**Genetic**
- Transcobalamin II deficiency

**Inadequate intake**
- Alcohol abuse
- Older persons
- Vegetarians (includes exclusively breastfed children of vegetarian mothers)

**Prolonged medication use**
- Histamine H2 blockers
- Metformin (Glucophage)
- Proton pump inhibitors
Clinical Manifestations of Vitamin B12 Deficiency

**Cutaneous**
- Hyperpigmentation
- Vitiligo

**Gastrointestinal**
- Glossitis
- Jaundice

**Hematologic**
- Anemia (macrocytic, megaloblastic)
- Thrombocytopenia

**Neuropsychiatric**
- Cognitive impairment
- Gait abnormalities
- Irritability
- Peripheral neuropathy
- Weakness
When you screen for B12 deficiency in a patient with macrocytic anemia you can measure:

Serum B12 (snapshot of what is your B12 level at the time of blood draw)

Methylmalonic acid (functional B12 assay that tells you what your B12 activity was in the past several weeks)

Homocysteine (functional test not only for B12 but also becomes abnormal in folic acid or B6 deficiency)
Methylmalonic acid metabolism
Fatty acids are broken down through the β-oxidation pathway that releases 2-carbon units in succession.

Fatty acid oxidation scheme works neatly for even-numbered chain lengths, it can't work completely for fatty acids that contain an odd number of carbons or Branched Fatty Acids
Decarboxylation → CO₂

Oxidation

β-oxidation here

Pristanic acid
Methylmalonyl-CoA isomerized by an epimerase and then by methylmalonyl-CoA mutase—an enzyme that uses Vitamin B$_{12}$ as a cofactor—to form succinyl-CoA, which is a TCA-cycle intermediate.
Hyperhomocysteinemia

While homocysteine levels are affected by both metabolic pathway polymorphisms and dietary methionine, additional factors include folate, vitamin B12, and B6 deficiencies; renal insufficiency; advancing age; male gender; and postmenopausal state.
Homocysteine is a product of genetic and environmental interactions. Produced by the demethylation of the amino acid methionine, homocysteine. Homocysteine can be remethylated to methionine, which requires a reduced form of folate as a methyl donor and vitamin B12 as a cofactor, or transsulfurated to cysteine, which requires the cofactor pyridoxine (vitamin B6).
### Pernicious anemia diagnostic cascade

<table>
<thead>
<tr>
<th>Vitamin B12 &gt;400 ng/L</th>
<th>Results do not suggest B12 deficiency-no further testing.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin B12 150 to 400 ng/L</td>
<td>Borderline vitamin B12 level-methylmalonic acid (MMA) is performed. If MMA is &gt;0.40 nmol/mL, then intrinsic factor blocking antibody (IFBA) is performed.</td>
</tr>
<tr>
<td>Vitamin B12 &lt;150 ng/L</td>
<td>Vitamin B12 deficiency-IFBA is performed. If IFBA is negative or indeterminate, then gastrin is performed.</td>
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<tr>
<td>MMA &lt; or =0.40 nmol/mL</td>
<td>This value implies that there is no vitamin B12 deficiency at the cellular level.</td>
</tr>
<tr>
<td>IFBA positive</td>
<td>Consistent with pernicious anemia, Graves disease, or Hashimoto thyroiditis.</td>
</tr>
<tr>
<td>Gastrin &gt;200 pg/mL</td>
<td>Result consistent with pernicious anemia.</td>
</tr>
<tr>
<td>Gastrin &lt;200 pg/mL</td>
<td>Result does not suggest pernicious anemia</td>
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</tbody>
</table>
The Schilling test is used to determine the etiology of vitamin B-12 deficiency in patients with normal IF antibodies.

**Stage 1:** Administer radiolabeled cobalamin 0.5-2.0 mCi PO to fasted patients. One to 6 hours later, administer unlabeled cobalamin 1000 mcg IM to saturate transcobalamin and flush hepatic storage. Measure the percentage of radiolabeled cobalamin in a 24-hour urine specimen. Urinary excretion within the reference range is 10-35% over 24 hours. Reduced urinary excretion of cobalamin, ie, less than 7-9% based on individual laboratory reference range values, in persons with normal renal function supports decreased absorption of oral cobalamin. If excretion is low, proceed to stage 2.

**Stage 2:** Stage 1 is repeated with coadministration of porcine IF 60 mg. If the absorption of cobalamin is normalized, the presumptive diagnosis is PA. If poor absorption persists after administration, proceed to stage 3.

**Stage 3:** Tetracycline is administered for 5 days prior to reperformance of stage 1 to exclude blind loop as the etiology.

**Stage 4:** Pancreatic enzymes are administered with repetition of stage 1 to test for pancreatic disease.

**Caveats:** If vitamin B-12 is administered 48 hours before the Schilling test, dilution of the radiolabeled cobalamin and spuriously low apparent urinary excretion and false-positive results occur. False-negative values occur in food-bound malabsorption due to achlorhydria. True negative results are from dietary deficiencies (vegan) and cobalamin binding–protein abnormalities.
There is a story passed among hematologists that after an American Society of Hematology annual meeting education session on B12 deficiency that explained in great detail the Schilling test, Dr. Schilling who was among the audience thanked the presenter and commented:

“My name is Dr. Schilling and I no longer use this test in clinical practice”
Oral Cobalamin for Pernicious Anemia: Medicine's Best Kept Secret?
Frank A. Lederle, MD
Presented at the annual meeting of the Society of General Internal Medicine, Washington, DC, May 2, 1990.
From the Department of Medicine, Minneapolis Veterans Affairs Medical Center, University of Minnesota.


Oral Cobalamin for Pernicious Anemia
Medicine's Best Kept Secret?
Effective treatment of cobalamin deficiency with oral cobalamin.

Kuzminski AM\textsuperscript{1}, Del Giacco EJ, Allen RH, Stabler SP, Lindenbaum J.

Randomly assigned 38 newly diagnosed cobalamin deficient patients with:

chronic atrophic gastritis
proven pernicious anemia
chronic omeprazole therapy for esophageal reflux
chronic H\textsubscript{2}-blocker therapy
inadequate dietary protein intake
prior ileal resection

Cyanocobalamin 1 mg intramuscularly on days 1, 3, 7, 10, 14, 21, 30, 60, and 90 vs. 2 mg orally on a daily basis for 120 days.
Between 1-2% of cyanocobalamin is absorbed by passive diffusion independent of intrinsic factor binding, so if you take 2,000 micrograms daily you will be absorbing at least 20-40 micrograms daily (e.g. 10 times the RDA)
Serum Methylmalonic Acid (nmol/Liter)

Months of Therapy

Normal range

Parenteral

Oral
Undoubtedly, parenteral treatment will continue to play a role in the treatment of cobalamin deficiency, particularly in hospitalized patients; in those with diarrhea, vomiting, or otherwise unable to take medication by mouth; in the unreliable; and in patients with severe neurologic involvement.

In the initial treatment of the average outpatient with mild to moderate deficiency or in patients who require maintenance therapy, oral cyanocobalamin with a preparation of proven bioavailability should be strongly considered, if not indeed viewed as the regimen of choice.
There may be an increased risk of gastric cancer, as well as gastric carcinoid tumors, in patients with pernicious anemia.

The prevalence of gastric neoplasia in patients with pernicious anemia, now considered to be associated with type A atrophic gastritis, is reported to be about 1% to 3% for adenocarcinoma and 1% to 7% for gastric carcinoid.

Most studies have shown an increased incidence of gastric cancer in patients with pernicious anemia on the order of 2 to 3 fold, although a large U.S. population-based cohort study found an incidence of gastric cancer of 1.2%, similar to that of the general population.

The risk seems to be highest within the first year of diagnosis.

A single endoscopy should be considered to identify prevalent lesions (gastric cancer, carcinoid tumors) in patients with pernicious anemia, but there are insufficient data to support routine subsequent endoscopic surveillance for these patients.
Cyanocobalamin is the most common vitamin $B_{12}$ produced (about 99% of the market) because cyanocobalamin is the easiest to crystallize and purify and is the most stable of the vitamin $B_{12}$ products.

Others include:

Hydroxycobalamin
Methylcobalamin
Many preparations/routes of delivery are available for vitamin B12 including:

- Oral
- Intranasal
- Sublingual
- Subcutaneous
- Intramuscular

IV use is discouraged as it is rapidly eliminated in the urine.

Recommended dietary amounts (RDAs) are 2.4 micrograms daily for ages 14 years and older, 2.6 micrograms daily for pregnant females, and 2.8 micrograms daily for breastfeeding females. Those over 50 years of age should meet the RDA by eating foods reinforced with B12 or by taking a vitamin B12 supplement.

Between 1-2% of cyanocobalamin is absorbed by passive diffusion independent of intrinsic factor binding, so if you take 2,000 micrograms daily you will be absorbing at least 20-40 micrograms daily (e.g. 10 times the RDA).
Can you get cyanide poisoning from too much B12?

Due to some articles going around the Internet, many patients have asked me whether vitamin B12 supplements in the form of cyanocobalamin are safe due to the cyanide content.

Data of from a Norwegian dietary survey show that the average and high (97.5th percentile) daily intake of cyanide among consumers amounts to respectively 95 and 372 micrograms/person or 1.4 and 5.4 micrograms/kg body weight/day.

The amount of cyanide in a 1,000 microgram cyanocobalamin is 20 micrograms which is about 0.6% of the amount that is thought to be the lower level that causes harm in a 70 kg adult.
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So which B12 preparation should you recommend?
Consider gummy bears for adults
Questions?

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