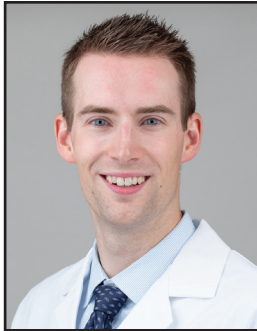
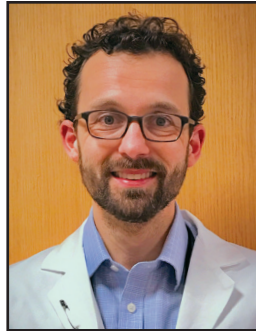


Carol Rees Parrish, M.S., R.D., Series Editor

Revisiting Vitamin B12 Deficiency: A Clinician's Guide For the 21st Century



Brian J. Wentworth



Andrew P. Copland

Vitamin B12 (cobalamin) deficiency is a common disorder encountered across various medical and surgical disciplines. In particular, the aging population, more widespread adoption of vegetarian and vegan diets, and rising utilization of bariatric surgery have increased the prevalence of this vitamin deficiency. Traditional diagnosis has relied on serum cobalamin quantification; however, accumulating evidence suggests that a significant proportion of cases are missed without additional workup. This review discusses the various etiologies of B12 deficiency, provides a practical approach to diagnosis, and summarizes the available nutritional and medical literature regarding management.

INTRODUCTION

Vitamin B₁₂ (cobalamin) is a water-soluble vitamin that serves as cofactor for three major cellular reactions converting:

1. Methylmalonic acid (MMA) to succinyl coenzyme A,
2. Homocysteine to methionine, and
3. 5-methyltetrahydrofolate to tetrahydrofolate.

Brian J. Wentworth MD, Fellow Physician, PGY-4, University of Virginia Health System, Division of Gastroenterology & Hepatology
Andrew P. Copland MD, Assistant Professor of Medicine, University of Virginia Health System, Division of Gastroenterology & Hepatology, Charlottesville, VA

The first reaction is a key step in the tricarboxylic acid (TCA) or Krebs cycle within the mitochondria to generate energy (adenosine triphosphate), while the latter two reactions ensure unimpeded DNA synthesis. In addition, vitamin B₁₂ (B₁₂) is essential for myelin synthesis and maintenance within the nervous system and also plays a role in bone marrow erythropoiesis.^{1,2}

B₁₂ deficiency is quite common. Estimates range from 40% to 80% in developing nations;³ surprisingly, approximately 6% of people aged less than 60 years and nearly 20% of adults older than 60 years are B₁₂ deficient in the United Kingdom and the United States.⁴ Despite its high prevalence, however, B₁₂ deficiency often remains undiagnosed and may present subtly in patients.

Table 1. Possible Etiology of Vitamin B12 Deficiency

Gastric	Intestinal	Pancreatic	Dietary	Medications	Congenital
<ul style="list-style-type: none"> Autoimmune gastritis (pernicious anemia) Surgery (e.g. gastrectomy, bariatric surgery) 	<ul style="list-style-type: none"> Ileal resection Active IBD SIBO Parasitic infection (e.g. giardiasis, fish tapeworm) 	<ul style="list-style-type: none"> Pancreatic insufficiency Gastrinoma (Zollinger-Ellison syndrome) 	<ul style="list-style-type: none"> Malnutrition Vegetarian Vegan 	<ul style="list-style-type: none"> Alcohol Acid suppressants (H₂RAs, PPIs) Metformin Colchicine Cholestyramine Nitrous oxide 	<ul style="list-style-type: none"> Imerslund-Gräsback syndrome (IF receptor defect) Transcobalamin deficiency

An understanding of the basic physiology of B₁₂ absorption will help the clinician contextualize how deficiency may develop. Appreciating the limitations of current diagnostic strategies is key to effective clinical practice.

Physiology

Vitamin B₁₂ is one of the essential vitamins as it cannot be synthesized by human metabolism. Bacteria and archaeobacteria synthesize B₁₂ through aerobic and anerobic pathways, respectively.⁵ Human colonic flora are also able to produce B₁₂, yet its location distal to the terminal ileum prevents absorption.⁶ To achieve an adequate daily intake of 2.4µg for adults (2.6µg for pregnant women and 2.8µg for lactating women), humans must obtain B₁₂ from animal products including meat, seafood, dairy, and fortified cereals.⁷ Interestingly, ≤1% of free cobalamin is absorbed at the epithelial border in the terminal ileum. The remainder is stored in the liver and muscles, with a half-life of 1-4 years.⁶

In food, B₁₂ is protein-bound. As food reaches the stomach, gastric parietal cells secrete pepsinogen and intrinsic factor (IF). Pepsin, the activated form of pepsinogen, cleaves food-bound B₁₂ allowing it to bind to haptocorrin (R-binder). In the small bowel, pancreatic proteases break this B₁₂-haptocorrin complex, forming a new B₁₂-IF complex. The B₁₂-IF complex travels to the terminal ileum where it is absorbed via the receptor complex cubam.^{6,8} After absorption, B₁₂ binds to either haptocorrin for transport to the liver, or transcobalamin to form holotranscobalamin, which facilitates incorporation into cells.⁸ In contrast, synthetic or unbound B₁₂ does not require pepsin to bind to IF and 1-2% can be passively absorbed

throughout the GI tract without intrinsic factor or the presence of an ileum.⁹

Both enteral nutrition (EN) and parental nutrition (PN) are able to provide adequate daily requirements for B₁₂, assuming the patient is on daily PN¹⁰ or receives the volume of EN needed to provide the daily requirement. A recent review of 62 enteral formulas determined on average each product provided > 200% of the recommended daily amount (doses of 1500 and 2000 Kcal/day).¹¹ Although jejunal feeding bypasses the stomach, the passively absorbed synthetic B₁₂ in commercial products is adequate to prevent deficiency.⁸

Pathophysiology

In addition to inadequate B₁₂ intake, there are numerous steps in the B₁₂ absorptive pathway where disease may strike (Table 1).

Gastric parietal cell loss secondary to autoantibodies (autoimmune gastritis) or surgical removal causes loss of hydrochloric acid and intrinsic factor production.¹² Autoimmune gastritis (AIG) has a prevalence of 2.5-12% without sex preference; all ages may be affected,¹³ but a large series reported a median age range of 70-80 years. It is associated with the presence of autoantibodies to parietal cells and/or intrinsic factor. Risk factors for development of AIG include a history of autoimmune disease (particularly thyroid disorders), northern European heritage, HLA DRB1*03 and DRB1*04 genotypes, and age over 30.¹⁴ Over time, pernicious anemia may develop, which is defined as the presence of anemia, low serum B₁₂, gastric body atrophy (with resultant atrophy of oxyntic glands and hypochlorhydria),

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Table 2. Factors Altering Serum Cobalamin, Methylmalonic Acid and Homocysteine Levels^{9,20,22-24}

Lab	Increase	Decrease
Cobalamin (B₁₂)	<ul style="list-style-type: none"> • Post-partum • Liver disease • Renal disease • Infection (e.g. HIV, malaria, typhus) • Inflammatory disease (e.g. rheumatoid arthritis) • Acute leukemia <ul style="list-style-type: none"> ○ Most commonly acute promyelocytic leukemia • Chronic myeloid leukemia • Myeloproliferative disorders • Primary hypereosinophilic syndrome • Solid tumors (lung, breast, GI, renal) • Lab variation (assay dependent) • Intrinsic factor antibodies 	Pregnancy
Methylmalonic acid (MMA)	<ul style="list-style-type: none"> • Renal disease • Small intestinal bacterial overgrowth (SIBO)† • Hypovolemia 	Pregnancy
Homocysteine (HCys)	<ul style="list-style-type: none"> • Folate deficiency • Renal disease • Hyperhomocysteinemia 	Pregnancy

†Increased MMA seen in SIBO secondary to excess bacterial propionate production, which is a precursor to MMA

and the presence of autoantibodies. The duration from onset of AIG to development of pernicious anemia is not well described in the literature, but some reports suggest a latency of as long as 20 years.²

Intestinal malabsorption of food-bound B₁₂ has several physiologic mechanisms, including ileal resection or active inflammation, pancreatic insufficiency, congenital defects (Table 1), and an altered intestinal microbiome.⁴ Small-intestinal bacterial overgrowth (SIBO) has increased in prevalence over time and may interfere with protein-bound B₁₂ absorption due to competitive inhibition by abnormal ileal flora.¹⁵

Some medications can also interfere with B₁₂ absorption. Chronic use (2+ years) of acid-suppressing medications, including H₂ receptor

antagonists (H₂RAs) and proton-pump inhibitors (PPIs), are associated with a higher likelihood of deficiency. The proposed mechanism involves a loss of gastric acid required to activate pepsinogen to pepsin in the stomach, disabling the cleavage of B₁₂ from its associated R-protein.¹⁶ Long-term metformin use has also been associated with B₁₂ deficiency; however, a true estimate of effect size remains elusive.¹⁷ Unlike acid suppressants, the mechanism for B₁₂ deficiency is less well understood for metformin, and may relate to interference of calcium-dependent membrane action necessary for B₁₂-IF complex absorption in the terminal ileum.¹⁸ Recreational nitrous oxide (N₂O) use in adolescent and young adult population may also precipitate B₁₂ deficiency with high dose or chronic

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Table 3. Diagnostic Performance of Combined Intrinsic Factor and Parietal Cell Antibodies in Patients with Atrophic Gastritis¹²

Subgroup	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
Low B ₁₂ , [†] macrocytic anemia, response to treatment	72.7	100	100	91.9
(Low B ₁₂ , [†] + iron deficiency anemia) OR (low B ₁₂ , [†] and macrocytosis [‡] with normal hemoglobin and response to treatment)	54.5	100	100	95.3
Normal B ₁₂ and normal hemoglobin	41.2	100	100	91.1
All Patients	60.6	100	100	80.9

†Defined as <190 pg/ml

‡MCV >100 fL

abuse. N₂O irreversibly oxidizes the cobalt ion of B₁₂, interfering with its ability to be a cofactor to methionine synthase, leading to downstream impairment of myelin production.¹⁹

Clinical Manifestations

The sequelae of B₁₂ deficiency in adults ranges widely in severity. Given the hepatic storage of inactive B₁₂, onset to overt deficiency may take up to 10 years.² Mild deficiency may present only as fatigue. As B₁₂ deficiency becomes more severe, skin hyperpigmentation, glossitis, cardiomyopathy and infertility can be seen.^{2,4} Thrombosis, including atypical presentations such as cerebral venous sinus thrombosis, may occur as a result of hyper-homocysteinemia induced by severe B₁₂ deficiency.²⁰

Bone marrow involvement is common and pancytopenia may develop in severe deficiency. Megaloblastic anemia is most frequently seen, although patients with AIG may initially demonstrate iron deficiency (gastric acid is necessary for duodenal iron absorption), before B₁₂ deficiency is diagnosed.²⁰

Neurologic dysfunction is not uniform and can present with demyelination of the posterior and lateral tracts of the spinal cord. Demyelination of these neurons causes both peripheral and

truncal weakness as well as paresthesias and a loss of vibration, pressure, and touch sensation. Progressive neurologic damage with untreated B₁₂ deficiency includes spastic ataxia, anosmia, ageusia, and optic atrophy.^{4,20} Peripheral neuropathy may also be seen, and in those with diabetes, it can be difficult to distinguish from diabetic polyneuropathy.²¹ Finally, at its most severe, B₁₂ deficiency may cause a dementia-like presentation termed “megaloblastic madness” with depression, mania, irritability, paranoia, delusions, and frank psychosis with hallucinations.^{4,20} Clinicians need to be aware that concomitant anemia in the presence of neurologic signs may be absent in up to 20% of cases and delayed diagnosis can lead to progressive and irreversible damage.⁴

Diagnosis

Making the diagnosis of B₁₂ deficiency requires attention to the limitations of current laboratory assays. Serum B₁₂ levels are often the first test performed, however these are subject to both false negatives and false positives. A severely low level (<100 µg/mL) is often associated with signs and symptoms of deficiency. Significant variation exists between various laboratory assays and B₁₂ levels may be spuriously normal or falsely high in patients

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Table 4. High-Risk Conditions for Vitamin B₁₂ Deficiency^{16,26-29}

Condition	Clinical pearls
Autoimmune thyroid disease	<ul style="list-style-type: none"> • 25% of patients have detectable parietal cell antibodies and 5% have intrinsic factor antibodies • 24% of these patients developed histologic-proven AIG after 5 yrs
Bariatric surgery	<ul style="list-style-type: none"> • Preoperative prevalence: 9-18% • Postoperative incidence 26-70% by 5yrs (most commonly ~33%)
Inflammatory bowel disease	<ul style="list-style-type: none"> • 2:1 prevalence in Crohn's disease vs. ulcerative colitis (33% vs. 16%) • Higher risk of deficiency if ileal resection of >20cm, active terminal ileal inflammation, small bowel skip lesions, or MRI evidence of pre-stenotic dilatation
Chronic medication use	<ul style="list-style-type: none"> • H₂RA: OR 1.25 of B₁₂ deficiency vs. controls with 2+ yrs of use • PPI: OR 1.65 of B₁₂ deficiency vs. controls with 2+ yrs of use (OR 1.95 if twice daily dosing) • Metformin: OR 2.45 of B12 deficiency vs. controls; mean lower levels of -66 pmol/L[†]

†Meta-analysis of 8000 patients; high heterogeneity secondary to non-standardized definitions of deficiency

with anti-intrinsic factor antibodies as intrinsic factor is often used in the U.S. as the assay-binding protein.²⁰ Thus, clinicians should consider the clinical context when interpreting serum levels and be careful to avoid direct comparison between two different values from independent laboratories (Table 2).

Elevated B₁₂

An elevated serum B₁₂ level is common. Prevalence ranges from 7-18% in hospitalized patients²² and does not necessarily exclude an underlying deficiency. The principle reason for a high level typically stems from an imbalance in B₁₂ plasma binding proteins (haptocorrin, transcobalamin) related to either increased synthesis or decreased clearance. In liver disease, damaged hepatocytes release B₁₂ in addition to abnormal hepatic clearance of haptocorrin. Elevated B₁₂ levels may be seen in various solid and hematological cancers, mostly secondary to high haptocorrin production. Additionally, renal dysfunction leads to poor B₁₂ clearance.^{8,22}

Methylmalonic Acid and Homocysteine

When clinical manifestations are subtle, measurement of serum methylmalonic acid (MMA) and homocysteine (HCys) can be helpful as they

reflect key cellular pathways involving B₁₂. Both MMA and HCys are elevated in >98% of patients with B₁₂ deficiency; HCys will also be elevated in folate deficiency. Both levels decrease rapidly after treatment and can be used to ensure adequate B₁₂ supplementation.²⁰

Limitations of MMA and HCys include falsely elevated levels in the presence of renal dysfunction,²⁰ variation in pregnancy without validated reference ranges,²⁴ and short-term fluctuations of MMA and HCys in both normal and deficient individuals.²⁵ There also is new evidence that polymorphisms in the gene HIBCH affect MMA levels irrespective of B₁₂ status.²⁴

Determining Etiology

Identifying the cause of B₁₂ deficiency aids in directing treatment. A detailed clinical history often reveals an obvious etiology such as vegetarian or vegan diets or patients with either gastric or ileal resections. The cumbersome Schilling test, involving administration of radioactive B₁₂ and measuring fractional urine excretion, has been phased out. Non-invasive assessment for AIG currently relies on detection of serum autoantibodies to parietal cells (PCAs) and intrinsic factor (IFAs). The combination of PCA and IFA often improves the characteristics of this testing¹² (Table 3).

Table 5. Vitamin B₁₂ Supplementation Regimens

Administration & Level of Evidence	Treatment & Maintenance Dosing	Pros	Cons
Intramuscular (<i>Strong †</i>)	<ul style="list-style-type: none"> Severe neurologic symptoms or anemia, severe malabsorption*: <ul style="list-style-type: none"> 1000µg daily or every other day for 1 week Then weekly for 4-8 weeks Then monthly for life (convert to maintenance) Mild malabsorption*: <ul style="list-style-type: none"> 1000µg daily or every other day for 1 week Then weekly for 4-8 weeks Then monthly for life <p><u>Maintenance:</u> 1000µg monthly</p>	<ul style="list-style-type: none"> Well-defined pharmacokinetics Useful for malabsorptive conditions Infrequent maintenance dosing 	<ul style="list-style-type: none"> Painful Frequency of initial dosing Non-adherence with long-term therapy
Oral (<i>Moderate ‡</i>)	<ul style="list-style-type: none"> Severe neurologic symptoms or anemia, severe malabsorption: <ul style="list-style-type: none"> 2000µg daily until resolution Mild malabsorption*: <ul style="list-style-type: none"> 500-1000µg daily or every other day for 1 week Then weekly for 4-8 weeks Then monthly for life <p><u>Maintenance:</u> 1000-2000µg/day</p>	<ul style="list-style-type: none"> Convenience Well-defined pharmacokinetics 	<ul style="list-style-type: none"> Daily dosing. Unclear role in malabsorptive conditions Non-adherence with long-term therapy Lower MMA normalization rates than IM therapy
Sublingual (<i>Weak *</i>)	<ul style="list-style-type: none"> 2000µg (2, 1000mcg SL tabs) daily for 7-12 days <p><u>Maintenance:</u> not defined</p>	<ul style="list-style-type: none"> Convenience Heterogeneous patient population 	<ul style="list-style-type: none"> Poorly defined pharmacokinetics Frequency of dosing
Intranasal (<i>Weak *</i>)	<ul style="list-style-type: none"> 1500µg (one puff of 750µg/70µL per nostril) at days 0, 14, and 21 <p><u>Maintenance:</u> not defined</p>	<ul style="list-style-type: none"> Convenience Infrequent dosing 	<ul style="list-style-type: none"> Poorly defined pharmacokinetics Limited patient population studied
Subcutaneous (<i>Anecdotal</i>)	Same as intramuscular	<ul style="list-style-type: none"> Less painful 	<ul style="list-style-type: none"> Poorly defined pharmacokinetics

*Conditions include: pernicious anemia, bariatric surgery, gastrectomy, ileal resection or reconstructive surgery, inflammatory bowel disease, congenital disorders (i.e. Imerslund-Gräsbeck syndrome)

*Conditions include: mild atrophic gastritis, medications (i.e. H2RA, PPI, metformin)

†Multiple meta-analyses, systematic reviews, randomized controlled trials

‡Cochrane review, randomized controlled trials

*Single center prospective non-placebo-controlled trials

However, the gold standard for diagnosis of AIG is endoscopy with biopsy. Elevated fasting serum gastrin and low serum pepsinogen may also be used to support diagnosis if uncertainty remains.¹⁴

Screening

No guidelines exist to assist clinicians with identification of patients at increased risk for deficiency and guide screening intervals. Nonetheless, clinicians should be aware of the high prevalence in certain key patient populations (Table 4). Expert opinion regarding several of these conditions suggests annual screening with a CBC and possibly serum B₁₂, MMA, and HCys.

Management

Treatment of B₁₂ deficiency has traditionally centered on increasing oral intake of food-bound B₁₂ and intramuscular (IM) injection of the synthetic vitamin. Cyanocobalamin is the preferred form of B₁₂ in the U.S., while hydroxocobalamin is primarily used in Europe; the latter formulation has been noted to have better retention and thus may be dosed less frequently.²⁴ Both are readily converted to the biologically active adenosylcobalamin and methylcobalamin.²⁴ Approximately 10-15% of a standard 1000µg IM B₁₂ injection is retained, allowing for rapid replacement.^{24,26} Guidelines from the British Society for Haematology recommend thrice weekly injections for two weeks in patients without neurologic deficits, with extension to three weeks or until clinical improvement if neurologic symptoms are present.² Injections may then be tapered to weekly for a month, then monthly in perpetuity if an irreversible cause is present. Improvement in MMA and HCys levels is seen within one-week; neurologic symptoms may take 6-12 weeks (sometimes with transient paradoxical worsening). Hematologic abnormalities may take up to eight weeks to normalize.^{2,20}

Oral replacement has become more popular in recent years given the cost, convenience, and pain associated with injection. For a similar 1000µg dose (as compared to IM), only 0.5-4% is absorbed.²⁴ A Cochrane review of the available evidence found no difference between serum B₁₂ levels in patients taking either IM or oral formulations (most commonly 1000µg/day). Outcomes related to signs and symptoms of deficiency or quality of

life were not reported in the trials reviewed.²⁶ Oral supplementation should ideally be administered in a fasting state as it is less effectively absorbed when taken with a meal.

Although there is some evidence for high dose oral supplementation in patients with known malabsorption or severe deficiency, most experts recommend IM administration. Treatment should be continued indefinitely if the etiology of malabsorption is irreversible – in patients with pernicious anemia who discontinue supplementation, neurologic symptoms recur as soon as 6 months; megaloblastic anemia can return within a few years.^{24,27} A prophylactic daily oral dose of 1000µg B₁₂ may be reasonable for patients having undergone bariatric surgery; in fact, this is recommended by the American Society for Metabolic and Bariatric Surgery.² Interestingly, despite the high prevalence in Crohn's disease, the recent American College of Gastroenterology²⁸ and American Gastroenterology Association guidelines²⁹ do not address specific recommendations regarding B₁₂ deficiency.

Other less common administration routes include sublingual³⁰ and intranasal,³¹ although the data supporting these modalities is derived from small cohorts of patients without severe clinical manifestations (or anemia in the sublingual cohort). There is anecdotal experience with successful subcutaneous (SQ) administration, however rigorous comparisons to IM have not been published. SQ injection is a preferred administration route by some patients at our institution, as they report less injection site pain as compared to IM. Table 5 provides a condensed summary of B₁₂ repletion strategies.

CONCLUSION

B₁₂ deficiency is common, yet under diagnosed, as clinical manifestations may be subtle. Serum B₁₂ levels can be problematic and clinicians should consider obtaining MMA and HCys to assist with diagnosis. Treatment can prevent irreversible neurologic damage. Fortunately, there are many therapeutic options for treating B₁₂ deficiency and maintaining adequate B₁₂ reserves. ■

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