

GUIDELINES & PROTOCOLS

ADVISORY COMMITTEE

Cobalamin (vitamin B₁₂) Deficiency - Investigation & Management

Effective Date: January 1, 2012

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BASICS

Introduction

Cobalamin is found exclusively in animal products such as meat, seafood, dairy products and eggs¹ (see *Appendix A: Dietary sources of cobalamin*). The recommended daily allowance of cobalamin is 2.4 mcg² (pregnant women 3.5 mcg), body stores are 2-5 mg, and the time to exhaust body stores is 2-5 years.

Dietary deficiency of cobalamin is rare except in long-term vegans. Food-Bound Cobalamin Malabsorption (FBCM) is seen in 20-40% of those >60 years of age.³ FBCM is caused by either lack of gastric acid,¹ or *H. Pylori* infection.⁴ Occasionally it can be seen in younger people especially those with long-term use of drugs (such as histamine (H₂) blockers, proton pump inhibitors, or metformin) or gastric resection.⁵ Lack of intrinsic factor due to autoimmune destruction of parietal cells is seen in pernicious anemia. A prospective survey of older adult North Americans (>60 yrs) revealed that 1.9% of the population had unrecognized and untreated pernicious anemia.⁴

Cobalamin deficiency leads to megaloblastic anemia and diverse neurologic symptoms like paraesthesias, numbness, poor motor coordination, memory lapses or cognitive and personality changes dorsal cord syndromes (bilaterally symmetrical ataxia, paraesthesias, proprioception abnormalities), and age-related cognitive impairment.

Scope

This guideline covers the investigation and management of cobalamin (vitamin B₁₂) deficiency in adults (≥19 years).

Risk Factors

Elderly people (>75-years)^{4,6} and long-term vegans are at risk of being cobalamin deficient.⁷

DIAGNOSIS

Who to test:

- Presentation: Unexplained neurologic symptoms, such as paresthesias, numbness, poor motor coordination, memory lapses or cognitive and personality changes. Anemia with features as described below.
- Laboratory findings: macrocytic anemia or macrocytosis with oval macrocytes or hypersegmented neutrophils or pancytopenia.

Consider testing:

- Demographics: elderly, i.e., >75 years
- Medical history: inflammatory bowel disease (of small intestine)
- Surgical history: gastric or small intestine resection
- Dietary history: prolonged vegan diet, i.e., no meat, poultry or dairy products
- Medication history: long-term use of H₂ receptor antagonists⁸ or proton pump inhibitors^{9,10} (at least 12 months), or metformin (at least 4 months)⁵

Routine screening for cobalamin deficiency is not indicated.

How to test

Perform a CBC, blood film and serum cobalamin in all patients suspected of cobalamin deficiency. Interpret serum cobalamin levels in light of clinical symptoms, because the test has the following limitations:

- It measures total, not metabolically active cobalamin.
- The levels of cobalamin do not correlate well with clinical symptoms. Elderly patients may have normal cobalamin levels with clinically significant cobalamin deficiency, while women taking oral contraceptives may have decreased blood cobalamin levels due to a decrease in transcobalamin, a carrier protein, but no clinical symptoms of deficiency.
- There is a large 'grey zone' between the normal and abnormal levels.
- The reference intervals may vary between laboratories. The conventional cut-off for serum cobalamin deficiency varies from 150-220 pmol/L.³ Using a more common cut-off of 220 pmol/L, the following interpretation is recommended:

Serum cobalamin (pmol/L)	Probability of symptomatic deficiency
< 75	High
75 - 150	Moderate
150 - 220	Low
>220	Rare

MANAGEMENT

Treatment

Early treatment of cobalamin deficiency is particularly important because neurologic symptoms may be irreversible.

- **Oral crystalline cyanocobalamin (commonly available form) is the treatment of choice. Dosing for pernicious anemia or food-bound cobalamin malabsorption is 1000 mcg/day. In most other cases a dose of 250 mcg/day may be used.**^{2,11-13}
- Oral administration of cobalamin is as effective as parenteral.^{4,14} (See Figure 1)
- Advantages of oral supplementation are comfort, ease of administration, and cost.
- Prophylactic cobalamin supplementation is recommended for strict vegans and patients with food bound cobalamin malabsorption, and for pernicious anemia.¹⁵
- Usefulness of prophylactic administration of cobalamin in elderly is unknown.⁴
- Parenteral administration should be reserved for those with significant neurological symptoms. It includes 1-5 intramuscular or subcutaneous injections of 1000 mcg crystalline cyanocobalamin daily, followed by oral doses of 1000-2000 mcg/day. Retest serum cobalamin levels after 4-6 months to ensure they are in the normal range.

Supplements

- Toxicity is minimal (especially with doses usually used in supplementation).¹⁶
- Oral supplements are available over the counter in various doses and dosage forms; prices will vary.
- PharmaCare coverage: Some PharmaCare plans* provide coverage for parenteral formulations (100 mcg/mL and 1000 mcg/mL)

*Coverage is subject to drug price limits set by PharmaCare and to the patient's PharmaCare plan rules and deductibles. See www.health.gov.bc.ca/pharmacare/ and <http://www.health.gov.bc.ca/pharmacare/benefitslookup/> Note: For complete details, please review product monographs and regularly review current Health Canada advisories, warnings and recalls at www.hc-sc.gc.ca for the most up to date information.

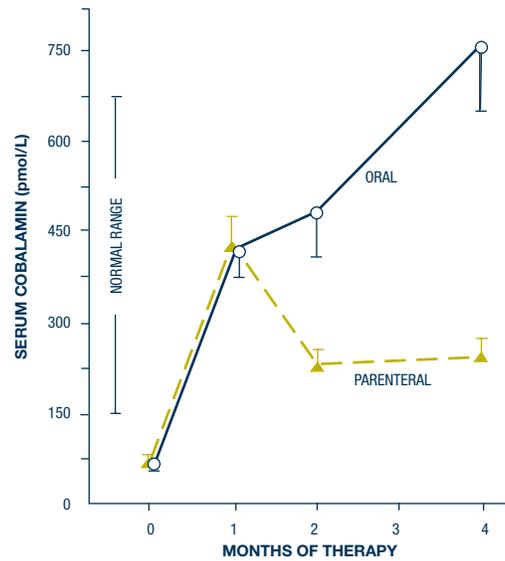


Figure 1. Mean serum cobalamin levels before and during 4 months of therapy with cyanocobalamin. Oral therapy was 2000 micrograms daily. Parenteral therapy was 9 injections of 1000 micrograms vitamin B₁₂ intramuscularly on days 1, 3, 7, 10, 14, 21, 30, 60 and 90. Bars indicate +/- 1 SEM. At 2 and 4 months, mean serum cobalamin concentrations were significantly higher with oral therapy ($p < 0.001$ and $p < 0.0005$ respectively).¹¹

ONGOING CARE

Duration of therapy

Patients with pernicious anemia require lifelong therapy, while patients with food-malabsorption require treatment until underlying condition or diet is corrected.

Monitoring

Annual testing of blood cobalamin levels is recommended in patients with non-nutritional cobalamin deficiency.²

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Abbreviations

FBCM - Food-Bound Cobalamin Malabsorption

H₂ - histamine

Diagnostic code

Serum cobalamin (B12) (92450)

Appendices

Appendix A: Dietary sources of cobalamin.

This guideline is based on scientific evidence current as of the Effective Date.

This guideline was developed by the Guidelines and Protocols Advisory Committee, approved by the British Columbia Medical Association and adopted by the Medical Services Commission.

A mobile version of this and other guidelines is also available at www.BCGuidelines.ca

The principles of the Guidelines and Protocols Advisory Committee are to:

- encourage appropriate responses to common medical situations
- recommend actions that are sufficient and efficient, neither excessive nor deficient
- permit exceptions when justified by clinical circumstances

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DISCLAIMER

The Clinical Practice Guidelines (the "Guidelines") have been developed by the Guidelines and Protocols Advisory Committee on behalf of the Medical Services Commission. The Guidelines are intended to give an understanding of a clinical problem and outline one or more preferred approaches to the investigation and management of the problem. The Guidelines are not intended as a substitute for the advice or professional judgment of a health care professional, nor are they intended to be the only approach to the management of clinical problems. **We cannot respond to patients or patient advocates requesting advice on issues related to medical conditions. If you need medical advice, please contact a health care professional.**

Appendix A: Dietary sources of cobalamin

Dietary Sources of cobalamin (B₁₂)¹ (RDA* 2.4 mcg, pregnant women 3.5 mcg)	
Food	mcg
Liver, beef, cooked 2½ oz	48.0
Clams, canned 2½ oz	74.2
Trout, rainbow, 2½ oz	5.6
Salmon, Pink, canned with bone 2½ oz	3.7
Tuna, light, canned in water, drained (2½ oz)	2.2
Salmon, Atlantic farmed, cooked 75 g (2 ½ oz)	2.1
Beef, regular ground, pan-fried 75 g (2 ½ oz)	2.3
Beef, regular ground, broiled 75 g (2 ½ oz)	1.4
Egg, chicken, boiled 2 large	1.1
Pork, loin, chop/roast, roasted (2 ½ oz)	0.9
¹ HealthLinkBC. [homepage on the internet]. [cited July 25 2011] Available from: www.healthlinkbc.ca * Recommended dietary allowance	