

# GUIDELINES & PROTOCOLS

## ADVISORY COMMITTEE

### **B<sub>12</sub> Deficiency – Investigation & Management of Vitamin B<sub>12</sub> and Folate Deficiency**

Effective Date: December 15, 2006

#### Scope

This guideline summarizes the current knowledge of the investigation and management of vitamin B<sub>12</sub> (cobalamin) and folate deficiency in adults.

#### Highlights

- **Oral vitamin B<sub>12</sub> is as effective as parenteral administration in treating B<sub>12</sub> deficiency in most cases**
- **As food in Canada is now fortified with folic acid, low blood folate levels are rarely encountered and routine ordering of folate tests is no longer justified**
- **Health Canada recommends that women planning pregnancy should consider a daily supplement of 0.4 mg folic acid beginning at least three months before conception to help reduce the risk of first occurrence of a neural tube defect. A recent study indicates adding other vitamins to folic acid may further reduce the incidence of neural tube and other birth defects<sup>1</sup>**

#### RECOMMENDATION 1

#### Indications for Investigation of Vitamin B<sub>12</sub> Deficiency

Vitamin B<sub>12</sub> deficiency may be suspected in the following circumstances:

- macrocytic anemia, or macrocytosis with oval macrocytes
- unexplained neurologic symptoms, such as paresthesias, numbness, or cognitive changes
- elderly people with poor diet and/or with neuropsychiatric symptoms
- vegan diet (long-term)
- inflammatory bowel disease
- history of gastric or small intestine surgery
- long-term use of histamine (H<sub>2</sub>) receptor antagonists or proton pump inhibitors

#### RECOMMENDATION 2

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

For investigation of suspected vitamin B<sub>12</sub> deficiency, measurement of serum vitamin B<sub>12</sub> is the standard test; however, it is important that serum B<sub>12</sub> levels be interpreted in light of clinical symptoms, because the test has the following limitations:

- It measures total, not metabolically active vitamin B<sub>12</sub>
- The levels are not easily correlated with clinical symptoms
- There is a large “grey zone” between the normal and abnormal levels
- The reference intervals may vary between laboratories and the results should be interpreted accordingly.

The conventional reference interval for serum vitamin B<sub>12</sub> is 150-600 pmol/L. Using this reference interval, the following interpretation is recommended:

Serum vitamin B <sub>12</sub> (pmol/L)	Probability of symptomatic deficiency
< 75	high
75 - 150	moderate
150 - 220	low
> 220	rare

Note:

1. Clinically significant vitamin B<sub>12</sub> deficiency may occur with vitamin B<sub>12</sub> levels in the normal range, particularly in elderly patients.
2. The most serious cause of vitamin B<sub>12</sub> deficiency is lack of intrinsic factor resulting in pernicious anemia. If pernicious anemia is suspected from history and clinical examination, consultation with a specialist is recommended.
3. Women taking oral contraceptives may have decreased blood vitamin B<sub>12</sub> levels, which may not represent a deficiency state; rather this may be due to a decrease in cobalamin-carrier protein.

**RECOMMENDATION 3**

Treatment of vitamin B<sub>12</sub> deficiency

**Oral replacement of vitamin B<sub>12</sub> is the treatment of choice in most cases, including pernicious anemia.** Patients with significant neurological symptoms, however, should receive initial intramuscular injections of 1000 µg vitamin B<sub>12</sub>, followed by oral doses of 1000-2000 µg/day. The duration of therapy depends on the cause of deficiency. In the case of pernicious anemia, treatment is life-long. Early treatment of vitamin B<sub>12</sub> deficiency is particularly important because neurologic symptoms may be irreversible.

**RECOMMENDATION 4**

Folate deficiency

Folic acid deficiency is associated with megaloblastic anemia<sup>2</sup> and birth defects (especially neural tube defects),<sup>1,3</sup> and may be associated with cardiovascular disease,<sup>4</sup> and certain types of cancer.<sup>5</sup>

- As all cereal-based foods in Canada are now fortified with folic acid, folic acid deficiency is rare. As less than one per cent of all folate tests are abnormal,<sup>(J.Heathcote, BC Biomedical Laboratories, D.Holmes, St. Paul's Hospital, personal communication)</sup> testing is rarely indicated.
- If folate deficiency is suspected, it is reasonable to give folic acid orally (3-5 mg/day) without doing laboratory investigation for deficiency.
- **Pregnant women and those planning to become pregnant should take 0.4 mg folic acid daily starting at least three months before conception and continuing throughout the pregnancy.**
- In suspected B<sub>12</sub> deficiency, folic acid alone should not be given as it may exacerbate/precipitate neurological symptoms.

## Rationale

Vitamin B<sub>12</sub> is found in animal products, primarily meat, seafood, dairy products and eggs.<sup>6</sup> Folate is found in a variety of foods, with the most common sources found in vegetables, fruit, cereals, and dairy products.<sup>6</sup> The recommended daily allowance of vitamin B<sub>12</sub> is 2.4 µg,<sup>7</sup> body stores are 2-5 mg, and the time to exhaust body stores is 2-5 years.<sup>2</sup> The recommended daily allowance of folate is 400 µg for an adult, and 600 µg during pregnancy.<sup>7</sup> Common food sources of vitamin B<sub>12</sub> and folate are found in Appendix 1.

Vitamin	RDA (µg/day)*		
	Men	Women	Pregnancy
Folate	400	400	600
Vitamin B <sub>12</sub>	2.4	2.4	2.6

Table adapted from: Health Canada – Dietary Reference Intakes, Reference Values for Vitamins

\*Health Canada RDA values are for normal apparently healthy adults (> 14 yrs age) eating a typical varied North American diet.

Vitamin B<sub>12</sub> deficiency is unusual among younger people except for strict long-term vegans.<sup>8</sup> Pernicious anemia is the most important result of vitamin B<sub>12</sub> deficiency; however, there has been some evidence for the association of vitamin B<sub>12</sub> deficiency and psychiatric problems in the elderly. A prospective survey of elderly (> 60 yrs) North Americans revealed that 1.9 per cent of the population had unrecognized and untreated pernicious anemia.<sup>9</sup>

Vitamin B<sub>12</sub> deficiency can occur due to inadequate intake or impaired absorption. Reduction in gastric acid production during aging probably accounts for most of the increased prevalence of vitamin B<sub>12</sub> deficiency with age, because gastric acid is required to release vitamin B<sub>12</sub> bound to proteins in food.<sup>10</sup> H. pylori infection<sup>11</sup> and long-term use of drugs that interfere with acid production such as H<sub>2</sub> blockers and proton pump inhibitors can also exacerbate deficiency.<sup>10</sup> In pernicious anemia, autoimmune destruction of parietal cells gradually decreases availability of intrinsic factor (IF) which is required for B<sub>12</sub> absorption. Gastrectomy or gastric bypass may also impede intestinal absorption due to reduction of intrinsic factor.

In patients with hematologic/clinical abnormalities suggestive of vitamin B<sub>12</sub> deficiency, serum vitamin B<sub>12</sub> should be measured. Patients with serum vitamin B<sub>12</sub> <75 pmol/L usually have clinical or metabolic evidence of vitamin B<sub>12</sub> deficiency.<sup>2</sup> In most patients with symptoms of vitamin B<sub>12</sub> deficiency, the serum vitamin B<sub>12</sub> level is below the reference interval (<150 pmol/L). However, it is estimated that between three to five per cent of clinical vitamin B<sub>12</sub> deficiencies occur in the range of 150-220 pmol/L and in some cases (0.2 per cent) can occur above this level.<sup>12,13</sup>

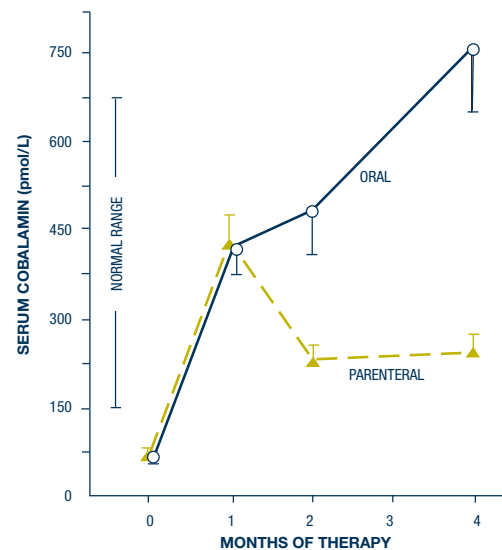
In most cases oral vitamin B<sub>12</sub> (1000 - 2000 µg/day) is as effective in treating vitamin B<sub>12</sub> deficiency as parenteral vitamin B<sub>12</sub>.<sup>14</sup> In such doses, a small but adequate portion of vitamin B<sub>12</sub> is absorbed even in the absence of intrinsic factor. Routine use of oral treatment in place of injection will reduce the costs of vitamin B<sub>12</sub> treatment considerably.<sup>15</sup> Patients with significant neurological deficit, however, should receive initial intramuscular injections of vitamin B<sub>12</sub>, followed by oral replacement. Timely treatment with vitamin B<sub>12</sub> is essential because cognitive dysfunction can be prevented by early intervention.<sup>16</sup>

Figure 1

Mean serum vitamin B<sub>12</sub> 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 B<sub>12</sub> 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).

Adapted from reference 14.



Folate deficiency can occur due to inadequate intake, increased demand (pregnancy, infancy), diseases where there is rapid cellular proliferation (i.e. haemolytic anemias), malabsorption, alcoholism, and drug interactions (i.e. anti-convulsants, oral contraceptives, sulfasalazine, methotrexate).<sup>2</sup> Folate deficiency is usually suspected when there is unexplained anemia, or macrocytosis.<sup>2</sup> With the implementation of folic acid fortification of foods in Canada, the average folate levels have increased significantly in the population, and consequently, folate deficiency is now uncommon. In two laboratories in British Columbia, 99.8 per cent and 99.1 per cent of folate tests were normal.<sup>J.Heathcote, BC Biomedical Laboratories, D.Holmes, St. Paul's Hospital, personal communication)</sup> When folate deficiency is clinically suspected, a therapeutic trial of folate may be considered without laboratory investigation for deficiency.<sup>2</sup> In rare cases of undiagnosed pernicious anemia resulting from vitamin B<sub>12</sub> deficiency, folate administration alone may exacerbate symptoms.

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## Sponsors

This guideline was developed by the Guidelines and Protocols Advisory Committee, and supercedes the guideline for vitamin B<sub>12</sub> and folate deficiency developed in July of 2003. This guideline has been approved by the British Columbia Medical Association and adopted by the Medical Services Commission.

**Revised Date:** April 1, 2007

This guideline is based on scientific evidence current at the time of the effective date.

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

## Appendix 1: Common Food Sources of Vitamin B<sub>12</sub> and Folate

<b>Dietary Sources of Folate (based on usual serving size)</b>		
<b>Excellent Source of Folate (55 µg or more)</b>	<b>Good Source of Folate (33 µg or more)</b>	<b>Source of Folate (11 µg or more)</b>
<ul style="list-style-type: none"> <li>• cooked fava, kidney, pinto, roman, soy and white beans, chickpeas, lentils</li> <li>• cooked spinach, asparagus</li> <li>• romaine lettuce</li> <li>• orange juice, canned pineapple juice</li> <li>• sunflower seeds</li> </ul>	<ul style="list-style-type: none"> <li>• cooked lima beans</li> <li>• corn, bean sprouts, cooked broccoli, green peas brussels sprouts, beets</li> <li>• orange</li> <li>• honeydew</li> <li>• raspberries, blackberries</li> <li>• avocado</li> <li>• roasted peanuts</li> <li>• wheat germ</li> </ul>	<ul style="list-style-type: none"> <li>• cooked carrots, beet greens, sweet potato, snow peas, summer or winter squash, rutabaga, cabbage, cooked green beans</li> <li>• cashews, roasted peanuts, walnuts</li> <li>• egg</li> <li>• strawberries, banana, grapefruit, cantaloup</li> <li>• whole wheat or white bread</li> <li>• pork kidney</li> <li>• breakfast cereals</li> <li>• milk, all types</li> </ul>

Table taken from: Health Canada. Nutrition for a healthy pregnancy: national guidelines for the childbearing years. Ottawa: Minister of Public Works and Government Services Canada, 1999.

Note: Food sources reflect naturally occurring folate and do not reflect folic acid content due to fortification.

<b>Dietary Sources of Vitamin B<sub>12</sub> (based on usual serving size)</b>		
<b>Excellent Source of Vitamin B<sub>12</sub> (35 µg or more)</b>	<b>Good Source of Vitamin B<sub>12</sub> (5 µg or more)</b>	<b>Source of Vitamin B<sub>12</sub> (1 µg or more)</b>
<ul style="list-style-type: none"> <li>• boiled or steamed clams</li> <li>• boiled or steamed oysters</li> <li>• braised veal liver</li> <li>• pan-fried beef liver</li> </ul>	<ul style="list-style-type: none"> <li>• baked or broiled herring</li> <li>• boiled or steamed crab</li> <li>• canned clam chowder</li> <li>• baked or broiled trout</li> <li>• cooked caribou (reindeer)</li> <li>• baked or broiled salmon</li> </ul>	<ul style="list-style-type: none"> <li>• omelette</li> <li>• milk (skim, partly skim, whole)</li> <li>• cheese (swiss, parmesan, cottage)</li> </ul>

Source: Adapted from Health Canada, Canadian Nutrient File, 1997.