Serum Vitamin B12 Testing: A Rapid Review

Health Quality Ontario

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Suggested Citation

This report should be cited as follows:


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Rapid Review Methodology

Clinical questions are developed by the Division of Evidence Development and Standards at Health Quality Ontario in consultation with experts, end-users, and/or applicants in the topic area. A systematic literature search is then conducted to identify relevant systematic reviews, health technology assessments, and meta-analyses; if none are located, the search is expanded to include randomized controlled trials (RCTs), and guidelines. Systematic reviews are evaluated using a rating scale developed for this purpose. If the systematic review has evaluated the included primary studies using the GRADE Working Group criteria (http://www.gradeworkinggroup.org/index.htm), the results are reported and the rapid review process is complete. If the systematic review has not evaluated the primary studies using GRADE, the primary studies included in the systematic review are retrieved and a maximum of two outcomes are graded. If no well-conducted systematic reviews are available, RCTs and/or guidelines are evaluated. Because rapid reviews are completed in very short timeframes, other publication types are not included. All rapid reviews are developed and finalized in consultation with experts.

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Background

Objective of Analysis

The objective of this rapid review was to establish under what circumstances, and how often, serum vitamin B12 tests should be used to assess vitamin B12 deficiency.

Clinical Need and Target Population

Description of Vitamin B12 Deficiency

Vitamin B12 is a water-soluble, essential vitamin. A deficiency in vitamin B12, which can occur due to inadequate absorption or intake, can lead to neurological, psychiatric, and hematological disorders. Foods that contain vitamin B12 include dairy and meat products. As a result, long-term vegans are at a higher risk of deficiency than others, and need to ensure they are choosing foods fortified with vitamin B12 or taking supplements. Vitamin B12 is stored for years in the liver, and a deficiency in vitamin B12 can occur slowly over time if B12 stores are depleted.

Causes of Vitamin B12 Deficiency

There are 3 main reasons a person becomes vitamin B12 deficient: (1)
- Inadequate dietary intake of vitamin B12
  - Strict vegetarianism (over the long term)
- Ineffective gastric breakdown of vitamin B12
  - Bacterial overgrowth syndromes
  - Fish tapeworm infestation
- Malabsorption of vitamin B12
  - Pernicious anemia
  - Gastrectomy or gastric bypass
  - Protein-bound cobalamin malabsorption
  - Ileal disease or resection
  - Pancreatic insufficiency
  - Drug induced (colchicine, neomycin, p-aminosalicylic acid, omeprazole)

Prevalence of Vitamin B12 Deficiency

It is unclear what the prevalence of vitamin B12 deficiency is in the general population. However, it is estimated to be between 2% and 6% in the United States. (2) Vitamin B12 deficiency is defined as a serum vitamin B12 level of less than 148 pmol/L. The prevalence of vitamin B12 deficiency is somewhat higher among the elderly (6-12%), (3;4) with an even higher prevalence among sick or institutionalized elderly (30-40%). (4) The prevalence of subnormal vitamin B12 levels (defined as a serum level between 148 pmol/L and 221 pmol/L) was estimated by 1 study to be around 20% in the elderly U.S. population. (3) Another study, however, based on the Framingham Offspring Study, reported that up to 39% of the U.S. population had subnormal serum vitamin B12 levels. (5)
Ontario Context

In the 2010/2011 fiscal year, more than 2.9 million serum vitamin B12 laboratory tests were billed to the province, at a cost of roughly $40 million. This was an increase over the number of tests performed in the 2005/2006 fiscal year, and was particularly marked in the community setting. (Table 1, Figure 1). One possible contributing factor was that, in 2007, the vitamin B12 test was added to the physician laboratory requisition form. The number of lab tests for vitamin B12 jumped by nearly 1 million between 2007 and 2008.

Table 1: Volume of Vitamin B12 Laboratory Tests in Ontario from 2005 to 2010

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>Hospital</th>
<th>Community</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>173,284</td>
<td>1,083,219</td>
<td>1,256,503</td>
</tr>
<tr>
<td>2006</td>
<td>199,412</td>
<td>1,188,066</td>
<td>1,387,478</td>
</tr>
<tr>
<td>2007</td>
<td>206,917</td>
<td>1,509,800</td>
<td>1,716,717</td>
</tr>
<tr>
<td>2008</td>
<td>222,136</td>
<td>2,436,765</td>
<td>2,658,901</td>
</tr>
<tr>
<td>2009</td>
<td>247,746</td>
<td>2,865,684</td>
<td>3,113,430</td>
</tr>
<tr>
<td>2010</td>
<td>255,620</td>
<td>2,651,992</td>
<td>2,907,612</td>
</tr>
</tbody>
</table>

Figure 1: Volume of Vitamin B12 Tests in Ontario from 2005 to 2010

Vitamin B12 test added to lab requisition form in 2007
Rapid Review

Research Questions

1. Who should be tested for vitamin B12 deficiency?
2. How frequently should patients with vitamin B12 deficiency be tested?

Research Methods

Literature Search

A literature search was performed on June 28, 2012, using OVID MEDLINE, OVID MEDLINE In-Process and Other Non-Indexed Citations, OVID EMBASE, EBSCO Cumulative Index to Nursing & Allied Health Literature (CINAHL), the Wiley Cochrane Library, and the Centre for Reviews and Dissemination database, for studies published from January 1, 2000, until June 28, 2012. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Inclusion Criteria

- English language reports
- published between January 1, 2000, and June 28, 2012
- systematic reviews, meta-analyses, and clinical practice guidelines
- investigated the assessment of measuring vitamin B12 levels

Exclusion Criteria

- studies investigating treatment or interventions for vitamin B12 deficiency
- randomized controlled trials, observational studies, case series, or editorials
- non–English language studies

Expert Panel

In August 2012, an Expert Advisory Panel on Appropriate Use of Vitamin B12, Folic Acid, and Iron Testing was struck. Members of the panel included physicians, personnel from the Ministry of Health and Long-Term Care, and representatives from community laboratories.

The role of the Expert Advisory Panel on Appropriate Use of Vitamin B12, Folic Acid, and Iron Testing was to contextualize the evidence produced by Health Quality Ontario and provide advice on the appropriate use of vitamin B12, folic acid, and iron testing in the Ontario health care system. However, the statements, conclusions, and views expressed in this report do not necessarily represent the views of Expert Advisory Panel members.
Results of Literature Search

The database search yielded 2,120 citations published between January 1, 2000, and June 28, 2012 (with duplicates removed). Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment.

In 2011, Willis et al (6) published a systematic review and meta-analysis of the diagnostic accuracy of the serum tests for assessing vitamin B12 (or cobalamin). They searched the literature from 1990 to 2009 and identified 54 studies for inclusion. They reported that there was no consistent reference standard used to measure the accuracy of the serum vitamin B12 test. They also reported a wide range of variability for sensitivity and specificity across the studies. For sensitivity, the range was 13% to 75%, and for specificity it was 45% to 100%. The authors (6) attributed the wide ranges to the inconsistent use of a reference standard.

Hvas and Nexo (7) also published an article regarding the diagnostic accuracy of serum vitamin B12 testing. Although their review was not systematic, they described the strengths and weaknesses of each vitamin B12 serum test. A summary of the tests based on the review of Hvas and Nexo (7) is listed in Table 2.

Table 2: Summary of Laboratory Tests Used to Assess Vitamin B12 Deficiency

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Rationale for Using the Test</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cobalamin</td>
<td>Decreases in vitamin B12 deficiency</td>
<td>Easily accessible $10 to $15 per test (in Ontario)</td>
<td>Sensitivity and specificity are questionable</td>
</tr>
<tr>
<td>Methymalonic acid (MMA)a</td>
<td>Increases with vitamin B12 deficiency</td>
<td>High sensitivity</td>
<td>Questionable specificity Roughly $105 per test</td>
</tr>
<tr>
<td>Total homocysteine (Hcy)a</td>
<td>Increases with vitamin B12 deficiency</td>
<td>High sensitivity</td>
<td>Low specificity influenced by lifestyle factors (smoking, alcohol consumption, coffee consumption) Roughly $65 per test</td>
</tr>
<tr>
<td>Holotranscobalamin (holoTC)a</td>
<td>Decreases in vitamin B12 deficiency Newer test, clinical utility unclear</td>
<td>High sensitivity</td>
<td>Specificity unclear</td>
</tr>
</tbody>
</table>

aThese laboratory tests are uninsured in community laboratories.

Three guidelines were identified on the diagnosis of vitamin B12 deficiency. There are countless guidelines on other conditions which indicate that serum vitamin B12 should be accessed, including but not limited to those for cognitive impairment (8), dementia (9), and Crohn’s disease (10).
The three guidelines (4;11;12) were assessed using the AGREE appraisal tool. (13) The assessment for each guideline is summarized in Table 3. Two of the guidelines were systematic reviews with recommendations. (4;12) These 2 reviews were published in peer-reviewed journals and described their methodology for the systematic literature search. The guideline by the British Columbia Medical Association and Ministry of Health was not explicitly based on a systematic review of the literature. In the methods that are reported on the website that published the guideline, the authors state that a full systematic review may not be conducted for all of their guidelines. As a result, it is unclear whether this guideline was based on the results of a systematic review. The British Columbia guidelines group has been contacted for further clarification.

All 3 guidelines scored poorly on linking the evidence to the recommendations.

**Table 3: AGREE Appraisal Summary for Each Guideline**

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Scope and Purpose</th>
<th>Stakeholder Involvement</th>
<th>Rigour of Development</th>
<th>Clarity of Presentation</th>
<th>Applicability</th>
<th>Editorial Independence</th>
</tr>
</thead>
<tbody>
<tr>
<td>British Columbia Medical Association/Ministry of Health, 2012 (11)</td>
<td>11</td>
<td>3</td>
<td>18</td>
<td>17</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Smellie et al, 2005 (12)</td>
<td>17</td>
<td>20</td>
<td>34</td>
<td>21</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Andres et al, 2004 (4)</td>
<td>10</td>
<td>6</td>
<td>27</td>
<td>21</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

The recommendations from each of the guidelines are listed in Table 4. The systematic review by Andres et al (4) used a flow chart or care pathway to describe recommendations. A notable difference in the guideline by Andres et al (4) was that the authors recommended screening all patients in institutions or psychiatric hospitals for vitamin B12 deficiency. This was not a factor in either of the other guidelines. Andres et al (4) reported that the prevalence of vitamin B12 deficiency was much higher (30% to 40%) in patients who were sick or institutionalized. As mentioned above, there was a very weak relationship between the recommendations and the evidence presented in all guidelines.
Table 4: Guidelines for the Assessment of Vitamin B12 Levels

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Populations for Testing</th>
<th>Frequency</th>
<th>Overall Recommendation</th>
</tr>
</thead>
</table>
| **British Columbia Medical Association/ Ministry of Health, 2012 (11)** | Patients with unexplained neurologic symptoms (parasthesia, numbness, poor motor coordination, memory lapses)  
Patients with macrocytic anemia or macrocytosis | Not reported          | Routine screening for vitamin B12 deficiency is not recommended |
| **Smellie et al, 2005 (12)**             | Patients with macrocytic anemia  
Patients with macrocytosis  
Patients with specific neuropsychiatric abnormalities | “There is no obvious merit in repeating vitamin B12 measurements unless lack of compliance is suspected or anemia recurs” | “Emphasize the importance of attempting to assess whether deficiency is present before requesting vitamin B12 levels ... assess medication, family history, diet, alcohol intake and symptoms of malabsorption” |
| **Andres et al, 2004 (4)**               | All elderly who are malnourished  
All patients in institutions and psychiatric hospitals  
All patients with hematological or neuropsychiatric manifestations of vitamin B12 deficiency | Not reported          | Not reported                                                |
Conclusions

- The volume of vitamin B12 tests increased substantially in Ontario when the vitamin B12 test was added to the laboratory requisition form in 2007.
- The serum vitamin B12 test has low diagnostic accuracy.
- Three guidelines on diagnosing vitamin B12 deficiency were identified, with limited evidence supporting the recommendations.
- Patients with symptoms or signs of vitamin B12 deficiency anemia (macrocytic anemia) should be tested for vitamin B12 deficiency. It is unclear whether other special populations should be tested for B12 deficiency (e.g., patients with suspect neuropsychiatric abnormalities).
- The frequency with which patients should be tested is unclear.
Acknowledgements

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Appendices

Appendix 1: Literature Search Strategies

Search date: June 28, 2012
Databases searched: OVID MEDLINE, MEDLINE In-Process and Other Non-Indexed Citations, EMBASE; Wiley Cochrane; Centre for Reviews and Dissemination (CRD) database

1. exp Vitamin B 12 Deficiency/ use mesz (9232)
2. exp cyanocobalamin deficiency/ use emez (5986)
3. exp Vitamin B 12/ or exp Transcobalamins/ use mesz (45211)
4. exp transcobalin/ or exp cyanocobalamin/ use emez (27433)
5. exp iron deficiency/ or exp iron blood level/ or exp iron overload/ use emez (19132)
6. exp Anemia/ (348498)
7. exp Hemochromatosis/ (16760)
8. exp Transferrins/ use mesz (19258)
9. exp transferrin/ use emez (20499)
10. exp ferritin/ or exp ferritin blood level/ use emez (39716)
11. exp Ferritins/ use mesz (15449)
12. exp Iron/ (167137)
13. iron overload.ti,ab. (13797)
14. (iron or hemochromatos* or ferritin* or cyanocobalamin* or transferrin* or b12 or b 12 or cobalamin* or transcobalamin* or holotranscobalamin* or holotc).ti,ab. (354035)
15. (an?emia* adj2 (b12 or b 12 or addison* or pernicious* or iron)).ti,ab. (22662)
16. or/1-15 (735822)
17. exp "Sensitivity and Specificity"/ (530170)
18. exp "Reproducibility of Results"/ use mesz (234104)
19. exp reproducibility/ use emez (127766)
20. exp "Predictive Value of Tests"/ use mesz (121365)
21. exp predictive value/ use emez (17963)
22. exp diagnostic accuracy/ use emez (160996)
23. exp Diagnostic Tests, Routine/ use mesz (6027)
24. exp Mass Screening/ use mesz (91380)
25. exp Screening/ use emez (368360)
26. exp Clinical Laboratory Techniques/ use mesz (1972392)
27. exp laboratory test/ use emez (100291)
28. exp Vitamin B 12 Deficiency/bl, co, di [Blood, Complications, Diagnosis] (4427)
29. exp cyanocobalamin deficiency/co, di [Complication, Diagnosis] (2061)
30. exp Anemia/bl, co, di [Blood, Complications, Diagnosis] (53169)
31. exp Hemochromatosis/bl, co, di [Blood, Complications, Diagnosis] (3207)
32. exp Hematologic Tests/ use mesz (196319)
33. exp blood analysis/ use emez (102122)
34. (sensitivity or specificity or screen* or diagnost* or ppv or npv or accuracy or clinical utility or predictive).ti,ab. (5465651)
35. exp Ferritins/bl, df, du, st [Blood, Deficiency, Diagnostic Use, Standards] (7435)
36. exp Vitamin B 12/ or exp Transcobalamins/ use mesz (4628)
37. exp transferrin/bl, df, du, st [Blood, Deficiency, Diagnostic Use, Standards] (617)
38. exp Risk Factors/ or exp case-control studies/ or exp cohort studies/ or exp cross-sectional studies/ use mesz (2398139)
39. exp Risk Factors/ or Cancer Risk/ or exp cross-sectional study/ or exp cohort analysis/ or exp case control study/ use emez (2442326)
40. or/17-39 (9540406)
41. ((elevated or raised or inadequate* or deficient* or insufficien* or high blood level* or high serum level* or high plasma level* or low blood level* or low serum level* or low plasma level* or suboptimal or sub-optimal or subnormal or sub-normal) adj (iron or ferritin* or cyanocobalamin* or transferrin* or b12 or b 12 or cobalamin* or transcobalamin* or holotranscobalamin* or holotc)).ti,ab. (3680)
42. 40 or 41 (9541738)
43. exp Technology Assessment, Biomedical/ use mesz (8702)
44. exp Biomedical Technology Assessment/ use emez (11295)
45. exp meta analysis/ use emez (63777)
46. exp Meta-Analysis/ use mesz (34386)
47. ((health technology* or biomedical technology*) adj2 assess*).mp. (14204)
48. (meta analy* or metaanaly* or pooled analysis or (systematic* adj2 review*)).mp. or (published studies or published literature or medline or embase or data synthesis or data extraction or cochrane).ti,ab. (324750)
49. or/43-48 (345143)
50. 16 and 42 and 49 (2630)
51. limit 50 to english language (2453)
References


