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## How do we evaluate a marginally low B<sub>12</sub> level?

### EVIDENCE-BASED ANSWER

The best way to evaluate a low-normal B<sub>12</sub> level is to check serum methylmalonic acid and homocysteine levels<sup>1</sup> (strength of recommendation [SOR]: **B**, based on consistent level 2 or 3 studies). Give

1 or 2 mg of oral vitamin B<sub>12</sub> a day if levels are marginally low and either methylmalonic acid or both methylmalonic acid and homocysteine are elevated (SOR: **A**).

### CLINICAL COMMENTARY

#### When faced with low-normal serum B<sub>12</sub>, either further evaluation or empiric treatment is warranted

With the advent of methylmalonic acid, homocysteine testing, and the proven efficacy of oral B<sub>12</sub>, medicine has come a long way from Shilling tests and monthly intramuscular shots in the diagnosis and management of B<sub>12</sub> deficiency. “Normal” serum B<sub>12</sub> may not accurately reflect true tissue B<sub>12</sub> stores. Therefore, if serum B<sub>12</sub> is borderline low, I routinely get methylmalonic acid and homocysteine for patients in whom I need to “prove” deficiency (for myself, patients, or third-party agents) or monitor closely (ie, those with neurologic symptoms).

Once deficiency is confirmed, search for a cause. Since 1000 mcg of oral B<sub>12</sub> treats nearly all causes of B<sub>12</sub> deficiency (including pernicious anemia and deficiency from gastric bypass surgery), empiric treatment is a reasonable alternative as long as serum B<sub>12</sub> and symptoms are monitored for therapeutic response. Bottom line: since early detection and treatment could potentially prevent permanent neurologic sequelae, when faced with a low-normal serum B<sub>12</sub>, it should not be dismissed as “normal”—either further evaluation or empiric treatment is warranted.

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### ■ Evidence Summary

A low-normal B<sub>12</sub> level is 150 to 350 pg/mL. Levels less than 150 pg/mL indicate deficiency. Levels greater than 350 pg/mL indicate adequate B<sub>12</sub> supply.<sup>2</sup>

Vitamin B<sub>12</sub> is a necessary coenzyme in the metabolism of methylmalonic acid to succinyl choline, and is also a necessary coenzyme with folate in the metabolism

of homocysteine to methionine. Therefore, a vitamin B<sub>12</sub> deficiency leads to elevated levels of unmetabolized methylmalonic acid and homocysteine. At a local lab the normal range of methylmalonic acid is 0.00 to 0.40 umol/L, and homocysteine’s normal range is 4.0 to 10.0 mmol/L. Normal levels might vary by laboratory. Other conditions, such as renal insufficiency, may

also cause elevation of methylmalonic acid and homocysteine.<sup>3</sup>

Holotranscobalamin may become a first-choice assay for diagnosing early vitamin B<sub>12</sub> deficiency. Studies have shown that it compares favorably with current combined measures (B<sub>12</sub> levels, methylmalonic acid, homocysteine). Like current assays, holotranscobalamin is also affected by renal function. It requires further investigation to establish relevant cutoff levels before it can be recommended as a diagnostic strategy.<sup>4</sup>

Oral vitamin B<sub>12</sub> at doses of 1000 to 2000 mcg/d is a simple and cost-effective treatment option for any B<sub>12</sub>-deficient person, and may actually be superior to intramuscular replacement.<sup>5,6</sup> A Cochrane Collaboration review of oral vitamin B<sub>12</sub> replacement found that these high doses seemed as effective as intramuscular vitamin B<sub>12</sub> in all B<sub>12</sub>-deficient patients—even those with pernicious anemia, Crohn's disease, ileal resection, or malabsorption states. The authors of the review recommend a "further large, pragmatic trial in a primary care setting" to determine whether oral vitamin B<sub>12</sub> is effective for patients with major common cases of malabsorption and to provide additional evidence for cost effectiveness.<sup>6</sup>

### Recommendations from Others

Current guidelines recommend giving vitamin B<sub>12</sub> if methylmalonic acid or both methylmalonic acid and homocysteine are elevated. Give folate if only homocysteine is elevated. Give vitamin B<sub>12</sub> if homocysteine elevation persists in spite of adequate folate replacement.<sup>2</sup>

Monitor for correction of low-normal B<sub>12</sub> and metabolites with follow-up blood test after 1 to 2 months of treatment. The negative predictive value of normal metabolites (methylmalonic acid and homocysteine) is unknown.

Individuals with normal vitamin B<sub>12</sub> levels and metabolites but significant B<sub>12</sub> deficiency signs and symptoms have responded dramatically to B<sub>12</sub> replace-

ment.<sup>7</sup> Therefore, it is reasonable to treat and monitor for response as an alternative approach to the evaluation of a low-normal B<sub>12</sub> level. Pennypacker et al<sup>2</sup> state that "the ultimate gold standard for vitamin B<sub>12</sub> deficiency may be the reduction in homocysteine and methylmalonic acid concentrations and improvement in clinical symptoms or signs in response to vitamin B<sub>12</sub> treatment."

### REFERENCES

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### FAST TRACK

**If serum vitamin B<sub>12</sub> is low, check homocysteine and methylmalonic acid levels; monitor patients with neurologic symptoms**