How do we evaluate a marginally low \( B_{12} \) level?

**Clinical Commentary**

When faced with low-normal serum \( B_{12} \), either further evaluation or empiric treatment is warranted

With the advent of methylmalonic acid, homocysteine testing, and the proven efficacy of oral \( B_{12} \), medicine has come a long way from Shilling tests and monthly intramuscular shots in the diagnosis and management of \( B_{12} \) deficiency. “Normal” serum \( B_{12} \) may not accurately reflect true tissue \( B_{12} \) stores. Therefore, if serum \( B_{12} \) 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 \( B_{12} \) treats nearly all causes of \( B_{12} \) deficiency (including pernicious anemia and deficiency from gastric bypass surgery), empiric treatment is a reasonable alternative as long as serum \( B_{12} \) 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 \( B_{12} \), it should not be dismissed as “normal”—either further evaluation or empiric treatment is warranted.

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**Evidence Summary**

A low-normal \( B_{12} \) level is 150 to 350 pg/mL. Levels less than 150 pg/mL indicate deficiency. Levels greater than 350 pg/mL indicate adequate \( B_{12} \) supply.

Vitamin \( B_{12} \) 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 \( B_{12} \) 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.¹

Holotranscobalamin may become a first-choice assay for diagnosing early vitamin B₁₂ deficiency. Studies have shown that it compares favorably with current combined measures (B₁₂ 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.⁴

Oral vitamin B₁₂ at doses of 1000 to 2000 mcg/d is a simple and cost-effective treatment option for any B₁₂-deficient person, and may actually be superior to intramuscular replacement.⁵,⁶ A Cochrane Collaboration review of oral vitamin B₁₂ replacement found that these high doses seemed as effective as intramuscular vitamin B₁₂ in all B₁₂-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 B₁₂ is effective for patients with major common cases of malabsorption and to provide additional evidence for cost effectiveness.⁶

**Recommendations from Others**

Current guidelines recommend giving vitamin B₁₂ if methylmalonic acid or both methylmalonic acid and homocysteine are elevated. Give folate if only homocysteine is elevated. Give vitamin B₁₂ if homocysteine elevation persists in spite of adequate folate replacement.²

Monitor for correction of low-normal B₁₂ 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 B₁₂ levels and metabolites but significant B₁₂ deficiency signs and symptoms have responded dramatically to B₁₂ replacement.⁷ Therefore, it is reasonable to treat and monitor for response as an alternative approach to the evaluation of a low-normal B₁₂ level. Pennypacker et al² state that “the ultimate gold standard for vitamin B₁₂ deficiency may be the reduction in homocysteine and methylmalonic acid concentrations and improvement in clinical symptoms or signs in response to vitamin B₁₂ treatment.”

**REFERENCES**


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