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

EVIDENCE-BASED ANSWER

The best way to evaluate a low-normal B_{12} level is to check serum methylmalonic acid and homocysteine levels[1] (strength of recommendation [SOR]: **B**, based on consistent level 2 or 3 studies). Give 1 or 2 mg of oral vitamin B_{12} 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_{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.[2]

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.[3]

Holotranscobalamin may become a first-choice assay for diagnosing early vitamin B_{12} deficiency. Studies have shown that it compares favorably with current combined measures (B_{12} 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 B_{12} at doses of 1000 to 2000 mcg/d is a simple and cost-effective treatment option for any B_{12}-deficient person, and may actually be superior to intramuscular replacement.[5,6] A Cochrane Collaboration review of oral vitamin B_{12} replacement found that these high doses seemed as effective as intramuscular vitamin B_{12} in all B_{12}-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_{12} 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 B_{12} if methylmalonic acid or both methylmalonic acid and homocysteine are elevated. Give folate if only homocysteine is elevated. Give vitamin B_{12} if homocysteine elevation persists in spite of adequate folate replacement.[2]

Monitor for correction of low-normal B_{12} 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_{12} levels and metabolites but significant B_{12} deficiency signs and symptoms have responded dramatically to B_{12} replacement.[7] Therefore, it is reasonable to treat and monitor for response as an alternative approach to the evaluation of a low-normal B_{12} level. Pennypacker et al[2] state that "the ultimate gold standard for vitamin B_{12} deficiency may be the reduction in homocysteine and methylmalonic acid concentrations and improvement in clinical symptoms or signs in response to vitamin B_{12} treatment."

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FAST TRACK

If serum vitamin B_{12} is low, check homocysteine and methylmalonic acid levels; monitor patients with neurologic symptoms