

How I treat

How I treat cobalamin (vitamin B₁₂) deficiency

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The challenges in medical management of cobalamin deficiency lie in attention to the unique pathophysiology that underlies cobalamin deficiency, more than in the mechanics of therapy. The central physiologic principles are that clinically important deficiency is more likely to occur (and progress) when intrinsic factor–driven absorption fails than when diet is poor and that most causes take years to produce clinically obvious deficiency. Transient defects have little clinical impact. The key management prin-

ciple is the importance of follow-up, which also requires knowing how the deficiency arose. The virtues of these principles are not always fully appreciated. Recent developments have made diagnosis and management more difficult by diminishing the ability to determine cobalamin absorption status. Clinicians must also grapple with premature medicalization of isolated, mild biochemical changes that added many asymptomatic cases of still undetermined medical relevance to their caseload, often expanded by inflated co-

balamin level criteria. The potential for misattribution of cobalamin-unrelated presentations to nongermane cobalamin and metabolite abnormalities has grown. Pathophysiologically based management requires systematic attention to each of its individual components: correctly diagnosing cobalamin deficiency, reversing it, defining its underlying cause, preventing relapse, managing the underlying disorder and its complications, and educating the patient. (Blood. 2008;112: 2214-2221)

Introduction

The discovery of a treatment for pernicious anemia (PA), a fatal disease until 1926, earned Minot and Murphy a Nobel Prize. With that advance, followed by identification of the defect in intrinsic factor (IF) secretion that defines PA and then synthesis of cyanocobalamin, cobalamin deficiency became relatively easy to diagnose and extremely easy to treat. It remained so until a decade ago.

Since the 1990s, a confluence of events and trends, some salutary but others unfortunate, has made clinical management of cobalamin deficiency more complex. Coming paradoxically at a time of remarkable biochemical and molecular advances and accessibility, the intimate linkage between the biochemical expressions and the pathophysiologic determinants of cobalamin deficiency frayed. These developments and their clinical consequences need to be addressed.

This paper has 3 goals. The first section reviews the essentials of pathophysiologically coherent management of cobalamin deficiency in adults. Where relevant, diagnostic issues are included because diagnosis is crucial to management, which has several coequal components. The second section assesses recent changes that have affected clinical care. The final section suggests approaches by clinicians to the influx of cases of subclinical cobalamin deficiency, about which clinically relevant information and consensus are lacking, and to preventive care.

Pathophysiologically based management of the cobalamin-deficient patient

The clinical encounter

The adult patient typically comes to medical attention because of symptoms related to anemia (such as fatigue), neurologic dysfunction (usually myelopathic or neuropathic, but occasionally also

cerebral or autonomic), and, rarely today, glossitis. Macrocytic anemia is the most common clinical finding,¹ with macrocytosis preceding the anemia by months,² but 13% to 27% of patients with PA have little or no anemia,^{3,4} and unrelated microcytosis masks the macrocytosis in 7% of anemic cases.⁵ A roughly inverse relationship often exists between hematologic and neurologic deficits.⁶⁻⁸ Some medical encounters occur solely because of a known predisposing gastrointestinal disease or, increasingly, an abnormal biochemical finding.

Serum cobalamin levels less than 200 ng/L (< 148 pmol/L), or less than 250 ng/L with some assays, are common, especially among the elderly,⁹ but approximately 22% to 30% of them are falsely low by both metabolic and clinical criteria,^{10,11} and most of the rest are clinically innocent.⁹ Their accidental coexistence with a suspected clinical finding can sometimes be misconstrued.¹² The initial task is to document the clinical and laboratory findings and prove their connection to cobalamin deficiency. Metabolic tests, such as serum methylmalonic acid (MMA) or plasma homocysteine, can be useful when the clinical picture is equivocal but are sometimes unreliable themselves.^{10,11,13} All samples must be obtained before cobalamin treatment effaces their value because cobalamin levels rise immediately and metabolites improve several days later.¹⁴

Reversing cobalamin deficiency

Cobalamin deficiency rarely requires instant therapy. Several days' delay to assure diagnostic certainty is acceptable even with neurologic symptoms, but treatment should be started expeditiously for severe neurologic symptoms with their risk of irreversibility (eg, extensive sensory defects, gait disturbances, mental changes).

Cobalamin therapy details. Table 1 summarizes relevant cobalamin details that provide physiologic context for discussions

Table 1. Cobalamin numbers that are useful in understanding cobalamin physiology, depletion, and therapy in adults

	Normal absorption	Malabsorptive disease (eg, PA)
Estimated daily loss/requirement	~ 1 µg/day	~ 2 µg/day*
Recommended daily allowance	2.4 µg/day†	Supplements are required
Average body stores of cobalamin	~ 2500 µg	Depends on stage of depletion
Ratio of stores to daily losses	2500:1	~ 1200:1‡
Amount (percentage) absorbed from a single oral dose of:§		
1 µg	0.56 µg (56%)	0.01 µg (1.2%)
10 µg	1.6 µg (16%)	0.1 µg (1.2%)
50 µg	1.5 µg (3%)	0.6 µg (1.2%)
500 µg	9.7 µg (2%)	7.0 µg (1.3%)
1000 µg	~ 13 µg (1.3%)	~ 12 µg (1.2%)
Amount (percentage) retained from a single injection of:¶		
10 µg	9.7 µg (97%)	Same as normal
100 µg	55 µg (55%)	Same as normal
1000 µg	150 µg (15%)	Same as normal

The data are summarized from the literature, especially from Chanarin¹ and Berlin et al.¹⁶ However, individual variation is wide, both in normal persons and patients with malabsorption.

*Daily losses presumably nearly double because of impaired reabsorption of biliary cobalamin in PA and other IF-related disorders (1.4 µg cobalamin is excreted in bile daily, of which half is presumably reabsorbed). The near-doubling of daily losses helps explain why deficiency progresses relatively more rapidly in PA than in disorders where IF-mediated reabsorption is preserved (eg, dietary insufficiency and, presumably, food-bound cobalamin malabsorption).

†IF-mediated absorption is only 50% to 60% of a small dose (ie, a normal meal). Thus, 2.4 µg should provide the daily 1-µg requirement but fails if the IF system does not function.

‡This estimate applies at the onset of the malabsorptive process. As stores become depleted, daily losses also decrease, but these changes, including the ratios, have not been quantitated.

§Based largely on data from Berlin et al.¹⁶ Note: (1) the reduced absorption rates in normal persons as oral doses escalate, (2) the constant 1.2% rate of nonspecific, IF-free cobalamin diffusion across the gut (clearly evident in patients with PA), and (3) the convergence of amounts of cobalamin absorbed by normal and malabsorbing persons the more oral doses exceed the capacity of IF.

¶Mean data compiled from Chanarin¹ and others. Variation among individuals is wide, however.

of doses and routes.^{1,15,16} I always begin with intramuscular cobalamin to bypass potential barriers to immediate effectiveness. A single injection, whether as an experimental 1- to 2-µg dose or the more usual 1000-µg dose, suffices to correct the anemia. The 1000-µg dose also begins repletion of stores (up to 150 µg is retained from that injection by most patients).¹ Cyanocobalamin, a pharmacologic preparation requiring conversion to metabolically active cobalamins, is the form commonly available in the United States, whereas hydroxocobalamin, which requires less frequent injections,^{1,15} is preferred in parts of Europe. Methylcobalamin, a light-sensitive form, is rarely used.

The toxicity of cobalamin is minimal, though not quite nonexistent. Allergic reactions are rare but can be anaphylactic.^{17,18} Injections seem more allergenic than pills and hydroxocobalamin may be more allergenic than cyanocobalamin, but reactions occur with all cobalamin forms (or the preservative) and routes. Changing preparations may not always solve the problem, and reevaluation under an allergist's supervision is advisable. Desensitization, antihistamines, and steroids have been tried with success.^{17,18} Depot injections, especially with hydroxocobalamin, sometimes induce autoantibody complexes with transcobalamin II and high cobalamin levels but no obvious clinical consequences. Whether hidden adverse effects lurk in the escalation of often unnecessary cobalamin use, especially with daily 1000-µg doses, is unknown. However, 16% of intracellular cobalamin in steady users of high doses was nonphysiologic cyanocobalamin, compared with 2% in nonusers.¹⁹

Emergency treatment. Therapeutic urgency never precludes starting a workup first. Even severe anemia does not require immediate cobalamin injection. After all, the anemia evolved over months, which allows compensatory increases in oxygen delivery. The elderly often tolerate hemoglobin levels as low as 5 g/dL surprisingly well while awaiting treatment.²⁰ Conversely, if symptoms or cardiovascular risks are alarming, cobalamin will not

suffice because hematologic response takes time. Such patients need immediate transfusion with packed red cells.

Transfusion should otherwise be avoided, unless dictated by clinical, not numerical, considerations.²⁰ Fluid overload is also dangerous. However, 2 widely quoted reports from a single source linking a unique 14% mortality with hypokalemia during cobalamin treatment for severe anemia²¹ reflect an association without causation that should be laid to rest. Plasma potassium often falls transiently when severe anemias respond to cobalamin (or iron), but its clinical relevance has never been proven. I found no early deaths in 101 severely anemic patients with PA who were not given potassium.²²

Initial therapeutic responses. Monitoring the response is surprisingly often left undone. A complete response provides ultimate confirmation of the diagnosis of cobalamin deficiency, and a blunted response allows early detection of complications.

Despite an unexplained sense of energy described by some patients in the first 24 hours, hematologic response only begins several days later.¹ The first objective landmark I rely on is the peak reticulocyte count 1 week after starting treatment. Its briskness should be proportional to the severity of the anemia. If reticulocytosis appears blunted, an incorrect diagnosis may be responsible, but I also obtain iron studies because coexisting iron deficiency is frequently obscured before cobalamin is given.^{1,23} The final hematologic landmark is that the blood count, including mean corpuscular volume (MCV), should be completely normal by the eighth week. A failure of homocysteine or MMA to normalize during the first week suggests an incorrect diagnosis,¹⁴ unless renal failure or other causes of metabolite elevation coexist. Cobalamin and holo-transcobalamin II levels are uninformative because they rise with cobalamin influx regardless of therapeutic effectiveness, the extent varying only with the timing in relation to injection.

Neurologic improvement begins within the first week also and is typically complete in 6 weeks to 3 months. Its course is not as

Table 2. Pathophysiologic characteristics of disorders that cause cobalamin deficiency

Characteristics and processes of cobalamin handling	Loss of intrinsic factor (IF; ie, PA)	Intestinal inability to absorb IF-bound cobalamin (eg, sprue)	Impaired food-bound cobalamin absorption (eg, gastritis)	Poor dietary intake of cobalamin (eg, veganism)	Defective cellular metabolism or uptake (eg, chronic N ₂ O toxicity)
Cobalamin intake	Normal	Normal	Normal	Low	Normal
Absorption of free cobalamin	Very low*	Very low*	Normal*	Normal	Normal except in transcobalamin II deficiency
Absorption of food-bound cobalamin	Very low	Presumably very low	Low	Normal	Normal except in transcobalamin II deficiency
Daily losses of cobalamin†	Increased	Increased	Presumably normal	Normal	Presumably normal
Likelihood of deficiency to progress	Very high	Usually high, but varies with disorder	Usually low, but varies with disorder	Usually low but varies	Usually high
Progression time to biochemical deficiency	< 2-5 years‡	< 2-5 years‡	Several years‡§	Several years‡§	Undetermined in most cases but probably brief
Progression time to clinical deficiency	2-5 years	2-5 years but may vary	Many years to decades§	Many years to decades§	Days, weeks, or months, depending on disorder

*Absorption of free cobalamin (cobalamin ingested free, as in crystalline supplements) depends on IF and its ileal uptake. The retention of normal ability to absorb free cobalamin differentiates food-bound cobalamin malabsorption from IF-based malabsorption (in which neither free nor food-bound cobalamin can be absorbed).

†The largest source of daily losses is the portion of biliary cobalamin not reabsorbed by IF.

‡Systematic data are not available, but biochemical expression (appearance of cobalamin and metabolite abnormalities) can precede clinical expression by a year or more, presumably. The lag between biochemical and clinical expressions may be even greater in the more slowly progressive disorders.

§Progression is slower than in IF-related malabsorption and may extend beyond a decade, but systematic data are lacking. More rapid progression may occur when other processes coexist.

predictable as hematologic response,^{1,4,7} but most studies show little advantage of more intensive cobalamin treatment. Recovery can be slow sometimes, but progression always calls for diagnostic reassessment. Patients with delayed improvement should be offered rehabilitative therapy, particularly for gait, urinary, or bowel dysfunction. Residual disability, estimated to affect 6% of neurologic patients,⁴ is the most feared outcome of cobalamin deficiency and is likely to persist if still present after 6 to 12 months of treatment. Irreversibility tends to be associated with more than 6 months of therapeutic delay,^{1,4} but its variability is unexplained. Most attention has focused on high folate status because of possible associations of adverse neurologic outcomes with folate therapy,^{1,2,4} but no consistent findings have emerged.

Finding the cause of the cobalamin deficiency

Cobalamin pathophysiology. The pathophysiology of cobalamin differs in important ways from most other vitamins, such as folate.²⁵ The daily requirement is so small relative to stores (Table 1) that deficiency typically takes years to develop in adults and only infrequently reaches the depletion point necessary for clinical consequences. Cobalamin is also tightly chaperoned everywhere by specific binding proteins and receptors that regulate how much traverses gut and other cell membranes, how much is reabsorbed after biliary secretion, and how much is retained by the body.²⁶ As long as specific absorption via IF remains intact, cobalamin economy is usually maintained. Transport defects at other sites are usually genetic and thus rare.

When IF is absent or its ileal uptake fails ("IF-related malabsorption," in shorthand for either failure), absorption of both free and food-bound cobalamin, as well as the daily reabsorption of approximately 50% of the 1.4 μg of biliary cobalamin,²⁶ fails (Table 2). As long as malabsorption persists, deficiency progresses, and clinical consequences may appear within "only" 2 to 5 years.

In more limited absorptive disorders, such as malabsorption confined to food-bound cobalamin (FBCM),²⁷ impaired cobalamin release from food limits but does not incapacitate the IF system, which also presumably continues reabsorbing biliary cobalamin. Some forms of FBCM remit after antibiotics.^{28,29} The rate of cobalamin depletion is unknown but is probably

many years slower than in IF-related disorders (Table 2). If the underlying disorder is nonmalabsorptive, such as dietary insufficiency, clinical consequences are delayed even longer^{30,31} because absorption and reabsorption are intact and because intake fluctuates. Only in rare disorders of cellular utilization do consequences appear rapidly (Table 2).

Not surprisingly, most adults who come to medical attention with clinically expressed cobalamin deficiency are those with IF-related malabsorption. Savage et al³² reported that 94% of patients with clinically expressed deficiency had IF-related malabsorption, such as PA or sprue; only 1% were vegetarians or had (presumptive) FBCM.

Clinical evaluation of absorption. Based on the foregoing, clinical signs of deficiency suggest IF-based malabsorption until proven otherwise. However, management decisions must be provisional until the disorder (which is often not PA) and its prognosis are identified (Table 3). For nearly 50 years, the diagnostic search began with the Schilling test, which not only identified abnormal IF-related absorption but also distinguished between gastric and intestinal defects. The underlying diseases themselves (eg, PA) are often asymptomatic and could not be detected otherwise.¹ An abnormal Schilling test result also helps select the optimal final test (eg, intestinal biopsy).

If the Schilling test result was normal, nonmalabsorptive disorders could be considered; so could FBCM, which the Schilling test cannot recognize but serves to rule out IF-related malabsorption as a diagnostic prerequisite for FBCM.^{27,33} A modified absorption test, in which the test dose of cobalamin is bound to food, was created specifically to identify FBCM.³³ However, because FBCM is relatively infrequently associated with clinical deficiency,^{27,32-36} the test never became clinically available,³⁷ even though FBCM is the most common disorder of cobalamin absorption and is associated with 30% to 50% of cases of subclinical deficiency.²⁷

Despite unwieldiness and occasionally uninterpretable results, the standard Schilling test had served clinicians well. Beyond its direct diagnostic benefits, an abnormal result strengthened the diagnosis of cobalamin deficiency, whereas a normal result prompted reevaluation of the diagnosis of deficiency itself. That being said, I usually tested for IF antibody upon documenting cobalamin

Table 3. Important diagnostic, therapeutic, and prognostic questions that depend on determining absorption status and identifying the specific disorder responsible for cobalamin deficiency

1. Is the deficiency likely to relapse? Must cobalamin replacement be lifelong, long term, or short term?*
2. If the deficiency is only subclinical when first diagnosed, is the deficiency likely to remain clinically silent or to progress to more serious deficiency?†
3. Should cobalamin replacement be done with periodic injection or large daily oral doses, or will small oral doses suffice?
4. Are all sources of oral cobalamin, or only food-bound cobalamin, absorbed poorly? Should supplements be taken on an empty stomach?‡
5. Are additional nutrient deficiencies likely to coexist and should they be sought?§
6. Does the underlying disorder require direct treatment itself? Can it be reversed?
7. Which cobalamin-unrelated complications of the underlying disease require independent action?¶ Do comorbidities or risks linked to the underlying disease exist?
8. If cobalamin absorption is normal, is the cause of the cobalamin deficiency then dietary, nitrous oxide-related, or a genetic disorder of metabolism or transport? Could the diagnosis of cobalamin deficiency itself be mistaken?

Data are modified and expanded from Carmel.³⁷

*PA is permanent and requires lifelong treatment. Some failures of intestinal uptake of IF may be treatable and even reversible. The course of FBCM is long, but it occasionally fluctuates.

†Mild or subclinical deficiency cannot be deemed innocuous if the underlying cause is early PA or other IF-related malabsorption. In contrast, most clinically silent deficiency is nonmalabsorptive in origin and unlikely to progress, and thus it may not need treatment.

‡Patients with FBCM may need to take cobalamin supplements on an empty stomach to prevent their binding to food in vitro; 1000- μ g oral doses appear necessary in many cases of FBCM, but it is not known whether giving such chronically high doses to others who do not need them can have undesirable effects.

§For example, broader malabsorption of additional nutrients is likely if intestinal disease is the cause and is less likely or limited to iron if the malabsorption is gastric in origin.

¶The risks of gastric malignancy and thyroid dysfunction in patients with PA require active screening. Such risks do not occur with other disorders.

deficiency. IF antibody has sufficient specificity for PA (> 95% as long as the blood is not drawn within a few days after injection) that the Schilling test could be omitted sometimes.

However, IF antibody sensitivity is poor (50%-70%), making the Schilling test necessary when antibody is absent. Serum gastrin and pepsinogen I abnormalities can sometimes help because of their high sensitivities for PA (90%-92%), but they lack specificity.³⁸ Even worse performance characteristics render parietal cell antibody diagnostically unhelpful for PA. With the loss of the Schilling test, I now combine the specific but insensitive IF antibody test with the sensitive but nonspecific serum gastrin or pepsinogen level in each cobalamin-deficient patient. None of these tests, nor any other blood tests, help diagnose intestinal malabsorption, FBCM, or nonmalabsorptive causes. With the loss of the Schilling test, each disorder must be pursued singly. The current muddle is a major setback to rational management, especially with the added burden of subclinical deficiency.³⁷

Preventing relapse of cobalamin deficiency: maintenance therapy

Maintenance regimens. Although I prefer injection in patients with IF-based malabsorption, the route and schedule are less important than a commitment to monitor closely. Whether given parenterally or orally, 1000- μ g doses are needed to accommodate wide variations in diffusion and retention among patients.^{15,16} The variations cannot be predicted but tend to remain consistent. Some patients describe feeling tired before the month is up; its attribution to “fast clearing” of cobalamin¹⁶ requires further study. Injection

intervals can be titrated or oral doses can be used as a bridge. I usually provide 8 to 10 injections over the first 2 to 3 months before considering monthly injections. This augments repletion and helps delay relapse should the patient discontinue treatment, as many do.⁶ Hydroxocobalamin injections can be spaced at twice the interval for cyanocobalamin.^{1,15}

Extensive long-term observations by Berlin et al¹⁶ documented a nonspecific, IF-unrelated diffusion of 1.2% (mean, with wide variation) of any oral dose. Thus, oral doses deliver much less cobalamin per dose once IF capacity (1-2 μ g) is exceeded in normal persons or is absent in PA (Table 1). Because of wide individual variations, 1000 μ g must be taken daily if malabsorption exists. Oral cobalamin is also less effectively absorbed after a meal than when fasted (1.8-7.5 vs 2.8-13.4 μ g of a 500- μ g dose).¹⁶ Small doses (5-10 μ g) are thought effective in cobalamin-deficient patients with normal Schilling test results. Responsiveness became murkier after blunted responses to oral doses less than 50 μ g were seen in some patients with FBCM.³⁹ Later studies reported blunted metabolic responses in many elderly persons with subclinical deficiency until doses reached 500 μ g or more⁴⁰⁻⁴²; these subjects' absorption status was not determined, however, and the pills were taken with meals in at least one study.⁴³

Parenteral vs oral maintenance in patients with malabsorption. Interest in oral therapy, proven effective in PA in the 1950s and 1960s,^{1,16} has revived, and 1000- μ g pills are now easily available and cheap. Despite the advantages in ease, cost, and comfort, physicians considering oral therapy should recognize its limitations, including possible disadvantages of dosing with meals.¹⁶ Physicians must also accept responsibility for adequate monitoring. The motivation and compliance of research subjects are unlikely to be matched in normal daily life. Moreover, relapse follows cessation of therapy months sooner after oral than parenteral regimens.^{7,16} Finally, even proponents report that many patients prefer monthly injections to daily pills or are neutral.^{16,44}

Many patients (or their trusted relatives) can be taught to inject themselves, which reduces cost to nearly that of oral therapy. With a 23-gauge or thinner needle and avoidance of deep injection, few patients complain of pain. I offer but do not encourage the option of oral maintenance therapy. Sublingual or nasal routes cannot be recommended because they are expensive and inadequately studied.

Monitoring and relapse. Some patients discontinue cobalamin once they feel better,⁶ often because they misunderstand the nature of their disease, but sometimes it is the physician who fails to think beyond the first shot. Relapse in patients with IF-related malabsorption occurs within 1 to 2 years.^{7,16} Either MMA or homocysteine is a better monitoring tool than serum cobalamin and provides early warning of relapse if measured annually.

Managing the underlying disease process

PA has cobalamin-unrelated issues. The most serious is a higher risk of gastric cancer and carcinoids.⁴⁵ Once the diagnosis of PA is confirmed, I encourage endoscopy to detect early, treatable lesions. If results are negative, routine reendoscopy does not appear worthwhile,⁴⁵ although it could be offered to young patients. Each patient with PA also needs periodic screening for thyroid disease and iron deficiency because of their high frequencies.^{23,46} Iron deficiency usually results from the atrophic gastritis, but other explanations are often found.

Management of ileal diseases is dictated by the specific entity, which is often treatable. Bacterial overgrowth of the gut responds to antibiotics but can recur if its underlying anatomic or motility disorder is irreversible. Pancreatic insufficiency can cause an

abnormal Schilling test result but is overemphasized as a cause of cobalamin deficiency.⁴⁷ The rarity of cobalamin deficiency in pancreatic insufficiency and some other known causes of cobalamin malabsorption, such as drugs, is probably explained by a need for uninterrupted, years-long malabsorption.

Partial gastrectomy is sometimes associated with IF loss and clinical deficiency^{1,32} but produces FBCM more frequently.³³ Bariatric surgery causes FBCM, as can atrophic gastritis with preserved IF^{27,28,33,39,48}; the resulting cobalamin deficiency is often subclinical, but prophylaxis may be warranted.^{39,48} Occasionally, FBCM can be reversed with antibiotics, which seems to happen with *Helicobacter pylori*-associated gastritis.²⁸ The association of *H pylori* with FBCM is unexplained, and many infected persons have normal absorption.⁴⁹ Reports of correction of cobalamin deficiency in *H pylori*-infected patients given antibiotics need better substantiation,⁵⁰ as does attribution of FBCM to upper small bowel bacterial contamination.²⁹

Education of the patient

One legacy of the misuse of cobalamin as a tonic for fatigue and other nonspecific symptoms⁵¹ has been misperception of the serious medical nature of clinical deficiency. Education helps prevent patients from abandoning treatment after achieving symptomatic improvement. The implications for prognosis and monitoring must be explained clearly, discussing lifelong therapy with those patients needing it, duration of therapy with those having reversible causes, and the need for follow-up with those whose underlying cause was not identified. It is useful to include family members in the discussion and to provide a written description of relevant facts. It also does not hurt to tell patients the grim history of PA before Minot and Murphy. Extra effort is needed for patients choosing oral therapy, who may confuse their therapy with optional self-supplementation.

Changes in concepts, tools, and practices

As noted in the Introduction, several developments have complicated the clinical management of cobalamin deficiency. One was the premature medicalization of mild, biochemical deficiency, followed by loosening of its diagnostic criteria.^{43,52} A second was the near-dismantling of the ability to determine who has cobalamin malabsorption and who does not.³⁷ The potential has grown for misattributing cobalamin-unrelated clinical findings to clinically irrelevant biochemical abnormalities.

Expansion and redefinition of cobalamin deficiency

The emergence of subclinical cobalamin deficiency. It was long known that some patients with low cobalamin levels (< 200 ng/L) lacked clinical evidence of deficiency. Schilling tests usually differentiated those with malabsorption, who received the diagnosis of very early PA, from those with normal absorption, who were deemed to have falsely low cobalamin levels. In 1985, we used deoxyuridine suppression testing to prove metabolic deficiency in patients with seemingly falsely low cobalamin levels^{36,53} and defined subclinical cobalamin deficiency.⁵⁴ Most patients were clinically normal, although some had subtle, asymptomatic, and still unexplained electrophysiologic and neurologic changes.^{36,55,56} The latter, like the metabolic abnormalities, reversed with cobalamin therapy. Many surveys, using homocysteine and MMA assays, soon proved subclinical deficiency to far outnumber clinical

Table 4. The effect of expanded serum cobalamin level criteria on the frequency of “suspected low serum cobalamin” in the elderly population

Country of study (year)	No. of subjects	Frequency (%) of “suspect” cobalamin in the elderly	
		Standard cutpoint (~ 200 ng/L)*	Revised cutpoint (~ 350 ng/L)†
United States (1994) ¹⁰	548	5.3	40.5
Netherlands (1998) ⁵⁹	105	24.8	60.1
United States (1999) ¹¹	591	11.8	50.4
England (2007) ⁷²	2,403	8.6	71.7

Data are from community-based surveys of medically unselected elderly populations with evaluable data.

*The standard cutpoints defining low serum cobalamin levels in the 4 studies were 200, 203, 190, and 203 ng/L, respectively.

†The expanded serum cobalamin cutpoints that were either recommended by study authors or are applied here solely for comparison purposes were 350, 352, 350, and 405 ng/L, respectively.

deficiency: 10% to 25% of the elderly had mild biochemical changes without symptoms, macrocytosis, neutrophil hypersegmentation, or Schilling test abnormality,^{9-11,54,57-59} whereas only 1.9% had PA.⁶⁰

Problematic consequences. Subclinical deficiency is still incompletely understood. It is often not differentiated from clinical deficiency or is assumed to be its prodrome despite rarely displaying IF-related malabsorption, the proven basis for 94% of clinical deficiency. The causes of subclinical deficiency remain largely unknown: diet is usually adequate,⁵⁷⁻⁵⁹ and FBCM was found in only 30% to 50% of cases.^{9,11,27,36,59} Neither its prognosis nor the health benefits of cobalamin therapy beyond biochemical normalization underwent prospective controlled study.⁴³ However, the course of subclinical deficiency often appears stationary.⁶¹⁻⁶³ The biochemical abnormalities themselves frequently fluctuate^{64,65}; mildly to moderately elevated MMA levels improved spontaneously in 44% of 432 cases retested 1 to 4 years later, and only 16% worsened.⁶⁴ Those observations notwithstanding, the impulse for medical intervention is such that controlled cobalamin trials in subclinical deficiency have been called unethical by some investigators.⁴²

Tinkering with “normality.” Strenuous efforts have been made to identify the earliest possible biochemical stigmata of deficiency. The investigators who patented the diagnostic application of metabolites to cobalamin deficiency took this one step further. Observing cobalamin levels above 200 ng/L in 2.9% to 5.2% of patients with clinical signs of deficiency⁶⁶ (in reality, an excellent 95%-97% sensitivity for the traditional 200-ng/L cutpoint), they raised the cutpoint to 350 ng/L.¹⁰ This redefinition transformed a 5.3% rate of suspected deficiency in their elderly volunteers to an astounding 40.5%.¹⁰ Only approximately 22% of the new suspects actually met MMA criteria for deficiency, less than 2% had macrocytosis, and none had evidence of PA.¹⁰

Despite the doubtful premise, the major loss of specificity, and the large, usually unrewarding clinical workload this portended (Table 4), many laboratories adopted the revised criterion. The potential clinical consequences merit illustration. Cobalamin testing is often done to rule out cobalamin deficiency as a cause of clinical symptoms and findings that mimic it. If 5.3% to 24.8% of the elderly population have cobalamin levels less than 200 ng/L (Table 4), so may 5.3% to 24.8% of elderly patients with alcohol-induced neuropathy or macrocytosis, which can be misattributed to those low cobalamin levels. With the redefinitions shown in Table 4, the risk of misdiagnosis jumps to 40.5% to 71.7%. In the end, clinicians must retain a cautious perspective on

Table 5. Suggestions for a clinical approach to asymptomatic, hematologically normal patients with suspected subclinical cobalamin deficiency

Notes	Comments
Diagnostic	
A low serum cobalamin (< 200 or 250 ng/L) is not automatically diagnostic for cobalamin deficiency in asymptomatic, hematologically normal patients.	22% to 30% of such cobalamin levels are falsely low.
A cobalamin level of 200 to 350 ng/L does not reflect cobalamin deficiency at all in 65% to 78% of such cases.	
At least two unrelated biochemical abnormalities should be sought to diagnose deficiency (eg, cobalamin and MMA) because an isolated biochemical abnormality (eg, MMA alone) may also be spurious, unless confirmed by its normalization with cobalamin therapy.	Results of all tests are unreliable in the face of renal insufficiency. Cobalamin and holotranscobalamin II values may be too closely linked to provide independent confirmation of each other.
Greatly elevated metabolite levels (eg, MMA >1000 nmol/L) require serious attention.	Mildly abnormal metabolite levels are often evanescent.
Always test for intrinsic factor antibody (despite its poor sensitivity) in a patient with suspected cobalamin deficiency.	Although PA is rare in subclinical deficiency, its diagnosis implies clinical disease and transforms management.
Therapeutic	
A monitored cobalamin trial is warranted for the patient with sufficiently suspicious clinical findings.	A cobalamin trial is not needed for a marginal, isolated metabolic abnormality unless compelling reasons exist.
The cobalamin trial should be parenteral. If given orally, 1000- μ g doses should be given daily for 4 weeks.	Injection or high oral doses are preferred because absorption often cannot be determined.
In a trial, clinical and laboratory reassessment should be done 4 to 8 weeks after injection.	Retest suspicious clinical findings as well as metabolic abnormalities.
Duration of therapy depends on the underlying disorder.	
Follow-up every 1 to 3 years is warranted in all patients with unknown causation or unclear course.	Follow-up should include clinical reevaluation and cobalamin and MMA assay.

isolated biochemical abnormalities in every context. A “gold standard” test does not exist, and neither homocysteine nor MMA elevation is conclusive proof of cobalamin deficiency.^{13,54,64}

The disappearance of cobalamin absorption testing

The value of absorption testing (Table 3) has been questioned sometimes on the misperceived grounds that PA always accounts for cobalamin deficiency (although PA explains only 76% of patients with clinical deficiency, and often treatable intestinal diseases account for 14%³²); that knowing the cause does not alter therapy (Table 3 to the contrary); or that testing for IF antibody is an adequate substitute (see “Clinical evaluation of absorption” for the inadequacy of surrogate tests). The use of the Schilling test began to decrease in the 1990s, perhaps influenced by such views but also by decreasing involvement of specialists, inadequate reimbursement for the test by insurers, and production concerns, including IF safety issues.³⁷ The test disappeared in 2003, leaving a severely limited ability to diagnose cobalamin malabsorption. Resurrection of the Schilling test with recombinant IF or creation of an equally validated direct test is needed.³⁷

Management modifications in current clinical practice

Management of subclinical deficiency

Until well-designed, placebo-controlled trials are done using health-related as well as biochemical endpoints in subclinically deficient persons, guidelines and algorithms for subclinical deficiency (ie, most low cobalamin levels) can only be tentative. This section, with Table 5, offers suggestions for an approach to subclinical deficiency by clinicians.

Suggested “rules.” (1) Current knowledge does not justify case-finding searches by clinicians for low cobalamin levels

without specific clinical indications. However, any abnormality discovered in a medical encounter must be pursued to clinically satisfactory resolution. (2) Low-normal cobalamin levels (250-350 ng/L) need not be pursued without clinical evidence of deficiency. The corollary, however, is that a clinically justified suspicion of deficiency must be pursued, whatever the cobalamin level. (3) The focus must always stay fixed on why the patient’s cobalamin level was measured in the first place. A therapeutic trial with appropriate endpoints is sometimes justified. (4) The presence of malabsorption has major clinical and prognostic relevance. I believe it may predict who requires intervention better than biochemical changes do.

A clinical approach to subclinical deficiency. The first clinical question is whether the patient is truly cobalamin deficient. The possibility that a seemingly subclinical deficiency is subtly clinical always needs consideration (eg, Is the normal MCV nevertheless higher than before? Does hypersegmentation exist?). Clinical deficiency often features serum MMA above 1000 nmol/L and homocysteine above 25 μ M.^{14,32,66} At the same time, because subclinically deficient patients are more likely than clinically deficient patients to have just one metabolite abnormality,^{10,11,14} and for it to be milder^{10,11} and to fluctuate,^{64,65} re-assay of marginally abnormal levels is advisable before proceeding any further. Abnormalities can also be cobalamin-unrelated (eg, renal failure). Normal metabolite results in an untreated patient without clinical or absorption abnormalities suggest a falsely low cobalamin level. Transcobalamin I (haptocorrin) deficiency, which may explain 15% of such cobalamin levels, should be considered in such cases.⁶⁷

The second clinical question is whether malabsorptive disease exists. All medically initiated encounters mandate this search. As insensitive as it is, IF antibody is the only credible test available for PA and should be obtained at the outset, with or without serum pepsinogen I or gastrin. If unrevealing, more invasive approaches (eg, gastroscopy, gastric analysis, small bowel testing) can be

weighed. If the patient had gastric surgery, FBCM is probable.^{27,33,39} Direct testing for FBCM is unavailable and surrogate markers are unreliable^{27,49}; the diagnostic sensitivities of gastrin and pepsinogen for FBCM are much lower than for PA (30%-32% vs 90%-92%).

The third clinical question is whether cobalamin therapy is indicated. Finding either IF-related malabsorption, which suggests a risk for progression, or signs suggesting mild but clinical deficiency justifies management as clinical deficiency. Patients suspected of FBCM require oral doses of 1000 µg daily, preferably on an empty stomach.³⁹⁻⁴² However, a nonmalabsorbing, asymptomatic patient with a lone, mild biochemical abnormality can be safely deferred for cobalamin or MMA reassessment a year later.

Patients whose status is inconclusive warrant a monitored therapeutic trial as the ultimate test. Two cobalamin injections can be followed 4 to 8 weeks later by a blood count parsed for subtle MCV improvement, reessay of the relevant metabolite, and reevaluation of whatever prompted cobalamin testing. Maintenance treatment is continued if response occurs but, unless underlying causes are identified, the requisite duration and prognosis are unclear.

Cobalamin prophylaxis in clinical practice

The value of general supplementation and the desirability and feasibility of dietary fortification with cobalamin are unproven.²⁵ Nevertheless, some situations call for targeted supplementation.

Vegetarians. Preventive supplementation is justified in strict vegetarians,³¹ including immigrants from the Asian subcontinent, whether or not they have liberalized their diets.³⁰ If small oral doses (eg, 2-6 µg) are ineffective, absorption should be evaluated. Physicians should be aware that surprisingly many vegetarians refuse supplementation.³⁰ Pregnant vegetarians who plan to exclusively breastfeed need supplementation; their babies are at much greater risk for severe deficiency than the mothers.⁶⁸

Patients with gastric surgery. The risk of FBCM and subclinical deficiency is high after subtotal gastrectomy³³ or bariatric

surgery.³⁹ Preventive supplementation with daily 1000-µg doses, preferably on an empty stomach, is warranted.

Elderly persons. Without very well-designed trials, routine cobalamin supplementation for the elderly has unknown value, even in the era of folic acid fortification.²⁵ Unnecessary folate supplements should be discouraged. Cobalamin status should be evaluated proactively in special situations.

Nitrous oxide (N₂O) exposure. N₂O inactivates cobalamin. When unrecognized and untreated clinical cobalamin deficiency (eg, PA) exists preoperatively, summation can produce rapid neuropsychiatric deterioration, especially after prolonged exposure.⁶⁹ Routine cobalamin and MCV testing is advisable before surgical or dental procedures involving N₂O exposure, especially in the elderly. Patients with abnormal results must be evaluated fully, and, if necessary, fully treated. Patients with conditions that predispose to deficiency, such as prior gastric surgery, should be treated by injection before surgery and by either route thereafter.

Clinicians should also be aware that N₂O is a popular agent for inhalant abuse in young people.⁷⁰ Repeated exposure can produce severe neuropsychiatric damage regardless of preexisting cobalamin status.⁷¹

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