TBM™ Brief:

Cobalamin

Kevin S. Millet, D.C.
Updated 9 May 2018

SPECIAL THANKS to the late Daniel L. Richardson, PhD (1942-2018) for his nudge into a seven-year cobalamin odyssey summarized below. His youthful exuberance and brilliance regarding human physiology, pharmacology, clinical nutrition, and herbology are sorely missed.

Background and Physiology

NOTE: The use of abbreviations, in order to conserve space, is extensive in this document. First use of such are in **bold** to facilitate location when a reminder of any particular abbreviation is desired. Thank you for your understanding.

Introduction

Cobalamin (Cbl), also known as vitamin B12, is a cobalt-containing, organometallic cofactor necessary for human life. The perspective that Cbl levels are adequate as long as **megaloblastic anemia (MA)** and/or severe neurologic pathologies are absent is fading as the awareness grows that essential physiologic processes are often impaired long before those conditions manifest. Humans possess two essential Cbl-dependent enzymes: **methylmalonyl coenzyme A mutase (MCM)** and **methionine synthetase (MeSe)**. MCM functions in the mitochondria and requires **adenosylcobalamin (AdoCbl)**, whereas MeSe functions in the cytosol and requires **methylcobalamin (MeCbl)**. Hence, AdoCbl is critical to DNA replication and MeCbl to methylation.

Cbl is synthesized by bacteria in the gut of ruminant animals and fish. Either the flesh or feces from those animals must be consumed by all other animals in order to acquire the Cbl needed for life processes. All of the following contribute to eventual Cbl-related depletion and/or dysfunction: failure to consume adequate Cbl-rich foodstuffs, digestive disturbances, certain auto-immune conditions, specific infections, certain genetic mutations, and exposure to nitrous oxide anesthetic (e.g. "laughing gas," "Whip-its").

Cbl-related dysfunctions can have broad-reaching clinical impacts in our patients. Therefore, we recommend a thorough evaluation of "all things cobalamin" for each patient. Information on how to conduct such an evaluation is taught in **Pathologies & Specialized Physiology – part one (PC1)** and described in our *PC1&2 (Module 3) Manual: 40th Anniversary Edition* available at www.liveTBM.com.

Safety of Cobalamin Augmentation

Cbl, a water-soluble vitamin, is absorbed in the healthy population via selective and/or active transport into cells. This not only includes the digestive tract but also cells throughout the body. Cbl has no known toxicity level, and excess Cbl is excreted via the stool and urine. Oral **cyanocobalamin (CN-Cbl)** is absorbed passively in those deficient in **gastric intrinsic factor (IF)** (i.e. pernicious anemia) when taken in therapeutic amounts. Supranormal serum Cbl levels have been observed concurrently with certain pathologies (e.g. cancer) and seem to offer a biologic defense mechanism against such pathologies, much like hyperthermia (fever) aids in controlling infections. Administration of extremely high levels of intramuscular MeCbl (45,000 mcg/week) for several months or longer has been shown to lead to the development of anti-cobalamin antibodies; however, no known adverse effects were reported.

Cobalamin Deficiency

There are two clinically-defined Cbl-depleted states in medical literature: clinical **Cbl deficiency (CD)** and **subclinical Cbl deficiency (SCCD)**. CD is associated with severe serologic changes, is reflected as MA and/or severe neurologic pathologies, and is caused primarily by **autoimmune gastritis (AIG)**, a.k.a. pernicious anemia. SCCD is associated with mild to moderate serologic changes and no apparent Cbl-related pathologies; it is primarily caused by **food-bound cobalamin malabsorption (FBCM)**. There is a third clinical entity alluded to in medical literature but not clearly defined: symptoms responsive to Cbl augmentation in the absence of Cbl-deficient serologic abnormalities. We have chosen to call this clinical condition **seronegative Cbl deficiency (SNCD)**.

NOTE: The incidence of CD in the elderly ranges from 20% in the general population to nearly 40% in those hospitalized. **Dietary Cbl insufficiency (DCI)** and FBCM must exist for 10-30 years before a Cbl deficiency becomes evident. DCI and FBCM together only account for 1% of CD. Atrophic gastritis manifests as CD in 2-5 years and accounts for 94% of CD etiologies. CD, as a result of N20 abuse, can occur within days but N2O abuse makes up less than 1% CD. FBCM is the cause of 30-50% of SCCD.

Most sensitive, literature-supported, guidelines in screening for clinical Cbl deficiency (CD) and subclinical Cbl deficiency (SCCD)		
Serum lab value	CD	SCCD
Total Cbl	<200 ng/L (<200 pg/mL)	<450 ng/L (<450png/mL)
MMA	≥ 750 nmol/L (≥ 0.750 µM)	≥ 271 nmol/L (≥ 0.271 µM)
Hcy	≥ 15 µM	≥ 10 µM
HoloTC	≤ 35 pmol/L	≤ 50 pmol/L

Cobalamin Synthesis

Cbl, in the form of **hydroxycobalamin (OH-Cbl)**, is synthesized to some degree by bacteria in the gut of nearly all animals when cobalt (Co) is present in the diet. However, in most animals, including humans, there is insufficient Cbl produced to meet physiologic requirements, and/or the Cbl is synthesized beyond the ileum and not absorbed. These such animals must consume flesh and/or feces containing Cbl. Commercially-produced Cbl is also synthesized by bacteria and is commonly in the CN-Cbl form due to its ability to withstand light and heat, which degrades OH-Cbl. Both OH-Cbl and CN-Cbl are readily converted to the metabolically active forms Ado-Cbl and Me-Cbl.

Cobalamin Management

Since Cbl is both a rare and fragile micronutrient, mammals possess a sophisticated protein chaperoning system that aids in ensuring dietary Cbl is protected from degradation by acid and gut microbiota; reserved until biologically needed; and irretrievably inert Cbl derivatives known as Cbl analogues, **corrinoids (CorA)**, or pseudovitamin B12 are excreted. Each Cbl chaperone only binds to a single Cbl molecule. **Salivary haptocorrin (HC)**, a glycosylated serum protein, is synthesized by myeloid cells and has a half-life of several days. It protects free Cbl from the low pH of the stomach once Cbl disassociated from protein by pepsin. IF shields Cbl from being consumed by intestinal biota—particularly E. coli—and presents it to the cubam receptor [**amnionless (AMN)/cubilin (CUBN)**] in the distal ileum for enteric absorption. Within the enterocyte lysosome, Cbl is disassociated from IF, allowing free OH-Cbl (or CN-Cbl if in supplemental form) to recouple with a protein chaperone, either HC or **transcobalamin (TC)**. The protein bound Cbl is then released into portal circulation. It largely bypasses the liver and enters directly into systemic circulation. TC is a

nonglycosylated serum protein synthesized primarily by enterocytes and the vascular epithelium and has a half-life of less than 2 hours. Once Cbl has served its intracellular metabolic functions, active transport mechanisms (e.g. ABCC-1 transporter) recycle Cbl back into systemic circulation, typically in the form of holoTC. Surplus Cbl is managed by four unique reserve mechanisms: hepatic, enterohepatic, serologic, and renal.

Hepatic Reserve

Approximately 50% of the body's 2-3mg of Cbl is found within the liver, primarily bound to MCM and MeSe. This **hepatic reserve** can supply 3 to 10 years of Cbl if none is provided in the diet and seems to be designed for a slow and sustained release when needed, as opposed to the renal reserve. The liver is the only known tissue that readily absorbs free Cbl and **holohaptocorrin (holoHC)**. It actively assimilates the latter via the **asialoglycoprotein receptor (ASGR)**, which is virtually exclusive to hepatocytes. Excess Cbl is either placed into systemic or enterohepatic circulation as holoHC.

Enterohepatic Reserve

Enterohepatic circulation (EHC) is the excretion by the liver of various substances (e.g. cholesterol, bilirubin, pharmaceuticals) in bile that are reabsorbed by the small intestine and returned to the liver via the portal vein and its tributaries. Each day, approximately 5-10 mcg of Cbl and CorA are released as holoHC in the bile. The holoHC is then lysed by pancreatic proteases (chymotrypsin, trypsin) in the small intestine. Free Cbl may then bind to IF and be taken up by the cubam receptor and transported back into to the systemic circulation as **holotranscobalamin (holoTC)**. Free CorA will rebind to HC and be eliminated as a constituent of feces; thus, EHC has a purifying effect. The liver contains 50 times the Cbl analogues as most other tissues due to being the sole tissue that possess a holoHC receptor. The **enterohepatic Cbl reserve (ECR)**, essentially a tube-like chamber that includes the biliary tree, small intestines and the portal vein [approx. 20 feet (6 meters)] contains a very significant amount of Cbl. In fact, if the ECR is not functioning (usually due to the absence of IF) the amount of time to CD reduces 10-fold (10-30 years to only 1-3)!

Serologic Reserve

The **serologic Cbl reserve** is the reservoir of Cbl circulating throughout the bloodstream as the non-biologically active protein-bound form holoHC. HC in the serum, as holoHC, is about 75% Cbl saturated, and holoHC makes up approximately 80% of the Cbl found in serum. Furthermore, HC binds both Cbl and CorA, so much of holoHC does not contain a biologically useable form of Cbl. The saturation of HC with CorA has been shown to be as high as 80%. TC is only about 10% saturated, as holoTC, and constitutes about 20% of serum Cbl. HoloTC is the only form of Cbl that can be taken up by the **megalin** and **transcobalamin II (TCblR/CD320) receptors** and, as such, is sometimes referred to as "Active-B12." While not yet available in the United States, it is easy to see that holoTC is the preferred measurement of serologic Cbl rather than the inaccurate total cobalamin.

Renal Reserve

The kidney, like the liver, is special when it comes to Cbl management. HoloTC is small enough (~40.0 kDa) to pass through the slits of the podocytes in the visceral epithelium of the glomerular capsule, thus allowing it to be filtered by the kidney. HoloHC is not. HoloTC is endocytosed by the **megalin receptor**, a calcium-dependent glycoprotein, in the apical plasma membrane of the proximal convoluted tubule epithelium. Once endocytosed the holoTC/megalin vesicle is coated with clathrin and taken into the lysosomes where it is digested by cathepsin B to yield free Cbl (OH, CN, Ado or Me-Cbl). The free Cbl remains stored in the lysosome until needed by the body. The megalin receptor is recycled back to the apical membrane and the TC spontaneously clears due to its short half-life (~90min). When the demand occurs, the stored Cbl will egress the lysosome via the **ATP-binding cassette transporter (ABCD4 aka ABCC1/MRP1)** into the cytosol. It is then released back into the tubule, along with renal synthesized HC and TC, where it is re-chaperoned, taken up by the distal tubule and placed into venous circulation. The kidneys, therefore, play the central role in Cbl management, providing a rapid-access reservoir. Free Cbl from the serum is quite rare. It is also filtered, but not reabsorbed, and will be excreted in the urine.

Vegetarianism

The most common cause of **dietary** Cbl deficiency is the **removal of animal flesh**, as in vegetarianism and veganism, resulting in not only the near absence of Cbl from the diet but also the diminishment of HCl production as a result of non-triggered gastrin hormone release. The diminished HCl secretion is further exacerbated by the effect hypochlorhydria has on mineral digestion, especially zinc, which is required for the production of HCl-producing carbonic anhydrase. Consequently, many former vegetarians and vegans remain hypochlorhydric and, therefore, remain Cbl deficient due to zinc deficiency and/or disuse-atrophy of gastrin-producing cells even though they have returned animal flesh to their diet.

Insufficient dietary Cbl intake (percentage)				
Sex		**Age**		
	19-24	**25-34**	**35-50**	**51-64**	**65-80**
Men	7.4	6.8	8.4	7.9	9.8
Women	32.7	26.4	24.5	23.0	26.3

Source: Gröber U, et al

Food-Bound Cobalamin Malabsorption

The most common cause of SCCD is FBCM, which has **many contributors**. **Abbreviated mastication** results in diminished surface area on which substrates may act. Inadequate mechanical and hydrolytic reduction of food particle size and inadequate blending of protease and haptocorrin (HC) reduces the likelihood that gastrically-liberated free Cbl will be able to combine with HC and form the R-protein complex needed to prevent acid deformation in the stomach. **Hypohydration**, chloride deficiency (**salt avoidance**), and **zinc deficiency** impair HCl production leading to **hypochlorhydria**. Keep in mind that HCL deficiency and IF deficiency are concomitants. The **cooking** of fish, seafood, beef, and lamb—all excellent sources of Cbl—reduces the raw Cbl content in these foods by up to 60%. These foods also become more difficult to digest after cooking. **Hyperacidity**, a frequent result of a chronic stress state, will also contribute to Cbl deficiency by increasing small bowel acidity and blocking the degradation of the R-protein complex. In order for the IF-Cbl complex to form, the R-protein complex must be broken down. The pancreas also plays a key role in Cbl absorption by

elevating the pH of chyme and supplying protease enzymes that are activated in a pH neutral environment. These proteases free the Cbl from the HC in the R-protein complex, thereby allowing Cbl to bind to IF. IF-Cbl is the only form of Cbl that will be endocytosed by the cubam receptor in the distal ileum. Therefore, **pancreatic insufficiency** not only dramatically reduces the absorption of dietary Cbl but also interferes with enterohepatic circulation, thereby depleting the entire body's Cbl supply. **Blind loop syndrome (BLS)** [aka stagnant loop syndrome, **small intestine bacterial overgrowth (SIBO)**], whose hallmark is E. Coli gut over-population, results in diminished Cbl due to E. coli consumption. One noteworthy contributor to the development of BLS is hypohydration due to the reduction of the small bowel mucin layer, a layer that is comprised of 90% water.

Autoimmune Gastritis

The most common cause of CD is **autoimmune gastritis** (pernicious anemia), where parietal cell antibodies destroy the parietal cell's capacity to produce HCl and IF. Decreased HCl production results in the inactivation of the stomach's principal proteolytic enzyme (pepsin), which is typically produced from pepsinogen and whose activity results in a liberation of the protein-bound Cbl through the denaturing of protein. Diminished IF production leads to a failure to produce an IF-Cbl pairing in the small bowel, thus providing the gut microbiota with the opportunity for unfettered consumption of Cbl. Prolonged **Heliobacter pylori-induced pangastritis** also leads to this outcome, and this condition is seen particularly in the elderly population.

Laboratory Diagnostics

Many **laboratory diagnostic tools** can provide useful insights into Cbl status and the status of Cbl-related parameters. This includes evaluation of: **gastric pH** (e.g. intragastric string test); SEROLOGIC MEASUREMENTS of Cbl [**total Cbl** (low sensitivity) and **holoTC** (high specificity and sensitivity)]; complete blood count (CBC) (low sensitivity, low specificity) [mean corpuscular volume (MCV), segmented neutrophils]; **methylmalonic acid (MMA)** (high specificity) (AdeCbl/mitochondria indicator) and **homocysteine (Hcy)** (high sensitivity) (MeCbl/cytosol); and potential causes of Cbl deficiency [**anti-gastric parietal cell antibodies, anti-intrinsic factor antibodies, anti-H. pylori antibodies** (particularly IgG)]. Since the Cbl levels necessary to prevent neurodegeneration are not yet agreed upon, **we recommend a multi-pronged approach to laboratory evaluation, which minimally includes total Cbl, MMA, Hcy and a complete blood count**. Where available, **HoloTC evaluation is also recommended**. Keep in mind that the incidence of SNCD is not known, is possibly very high, and that Cbl augmentation is inexpensive, easy-to-implement and very safe. This is where Need & Use evaluation can be especially beneficial.

> "Minimal concentrations of serum vitamin B12 for optimal neuronal health are still unknown…Though serum cobalamin is a valuable marker of cobalamin deficiency, a number of neurologic disorders have been attributed to cobalamin deficiency in spite of normal or minimally reduced serum cobalamin concentrations…In clinical practice, normal concentrations of serum B12 do not exclude the diagnosis of B12 deficiency." Source: Rizzo G et al. (2016)

NOTES: Cbl therapy in the presence of macrocytic anemia, as a result of decreasing the size of serum erythrocytes, will result in a fall in serum iron within 1 to 2 days. Iron levels will, however, shortly return to normal unless a true iron deficiency exists. Cobalamin is a near neurologic panacea. We encourage every health care provider to consider the value

of Cbl augmentation in every patient with any neurologic/neuropsychiatric symptom. Keep in mind that the longer the duration of neurologic symptoms the worse the prognosis. However, the severity of Cbl deficiency, gender, and age have not been shown to have a negative impact on the prognosis. Irreversibility of neurologic symptoms is considered to occur within only a six-month delay in the onset of therapy. Normalization of MMA and Hcy occurs after about 1 week after the onset of Cbl augmentation. Normalization of CBC requires about 2 months. Neurologic improvement begins to become apparent in about 1 week and is complete within 3 months.

Causes of Cobalamin Deficiency

Gastrointestinal

Autoimmune atrophic gastritis (pernicious anemia) (AAG) (incidence is ≈ 20% 16-59 year olds, ≈30% 60-69, ≈40% 70, ≈80% 80), blind/stagnant loop syndrome [aka small bowel bacterial overgrowth (SIBO)], achlorhydria, hypochlorhydria, pancreatic protease insufficiency, celiac disease, ulcerative colitis, ileocecal resection, total or partial gastrectomy, gastric bypass surgery, H. pylori infection, exocrine pancreatic insufficiency [insufficient pancreatic proteases (enterokinase-dependant trypsin and trypsin-dependent chymotrypsin) and bicarbonate], intestinal enterokinase deficiency (small bowel villous atrophy), gastric acid hypersecretion, prolonged steatorrhea, pancreatitis (acute or chronic), biliary obstruction (lack of bile salts resulting in saponification of calcium and impairment of Cbl absorption), bile insufficiency, biliary dyskinesia, calcium deficiency, functional pancreatic insufficiency, Sjogren's syndrome, Crohn's disease, Whipple's disease, intestinal lymphoma, intestinal tuberculosis, Diphyllobothrium latum (fish tapeworm) infection.
NOTE: IF and HCl are concomitants, therefore if HCl is deficient or absent so is IF.

Dietary

Vegetarian diet, vegan diet, hypohydration, salt avoidance, zinc deficiency, dependence on liquid proteins, insufficient mastication, chronic alcohol abuse (alcoholism), ascorbic acid (vitamin C) megadosing.

Pharmacologic

Prolonged use of the following: H2 antagonists (e.g. Pepcid, Tagamet, Zantac), proton pump inhibitors (e.g. Prilosec, Prevacid, Nexium), biguanides (e.g. Avandia, Actos, metformin), oral contraceptives, gentamicin, cholestyramine, anticonvulsants, colchicine, direct (e.g. surgery, dentistry, "whip-its") and indirect (e.g. dental and anesthetic attendants) nitrous oxide (N20) exposure. NOTE: Nitrous oxide anesthesia can trigger neurological damage and hematological deficiencies in patients who have Cbl deficiency and should, therefore, not be administered in a patient of questionable Cbl status without serologic screening first.

Genetic

There are many Cbl-related single nucleotide polymorphisms (SNPs). For more information on them we refer you to the COBALAMIN-RELATED SNPs section in our *PC1&2 (Mod 3) Manual: 40th Anniversary Edition* available at www.liveTBM.com.

Other
AIDS, amyloidosis, scleroderma.

Indications of Cobalamin Deficiency

Neurological Symptoms
Dyscognition, nocturia, myelopathy, neuropathy, dementia, optic nerve atrophy, **subacute combined degeneration (SCD)** (myelosis funicularis), symmetric dysesthesia, disturbance of position sense, spastic paraparesis or tetraparesis, isolated peripheral neuropathy, slowed mentation, memory impairment, attention deficits, bilateral visual loss (scotoma), paresthesia, numbness, autism, autism spectrum, schizophrenia, peripheral neuropathy, hyporeflexia, Babinski's sign, ataxia, Rhomberg's sign, anxiety, learning disabilities, polyneuritis, ataxia, cranial nerve abnormalities (e.g. optic neuritis, optic atrophy, urinary and fecal incontinence), Parkinson's disease, depression, anorexia nervosa, venous thromboembolic disease, angina, delirium, hallucinations, mania, delusions, personality change, abnormal behavior, brain atrophy, silent brain infarcts, dysautonomia, psychosis (suspiciousness, persecutory delusions, religious delusions, auditory hallucinations, visual hallucinations, tangential or incoherent speech, disorganized thought-process).

Hematological Symptoms
Angor, angina, dyspnea on exertion, fatigue, congestive heart failure, ankle edema, orthopnea, thrombocytopenia, neutropenia, pancytopenia, hemolytic anemia, thrombotic microangiopathy, stroke, atherosclerosis, medullary megaloblastosis ("blue spinal cord"), leukoaraiosis, orthostatic hypotension.

Dermatological Symptoms
Premature graying of hair, vitiligo, glossitis, aphthous stomatitis, angular stomatitis, cutaneous hyperpigmentation, longitudinal melanonychia, alopecia areata, alopecia totalis, poliosis, jaundice, mucocutaneous ulcers.

Gastrointestinal Symptoms
Abdominal pain, dyspepsia, nausea, vomiting, diarrhea, irritable bowel syndrome, constipation.

Genitourinary Symptoms
Vaginal dryness, vaginal infection, urinary tract infection, hypofertility, infertility, repeated miscarriages, impotence, micturition, nocturia.

Serological Findings
Decreased total Cbl, decreased holoTC, elevated Hcy, elevated MMA, macrocytic megaloblastic anemia, increase of mean corpuscular volume, neutrophil hypersegmentation, elevated lactic dehydrogenase (LDH), elevated bilirubin.

Magnetic Resonance Imaging (MRI) Findings
Symmetrical abnormally increased T2 signal intensity confined to posterior or posterior and lateral columns in the cervical and thoracic spinal cord, spinal cord sclerosis.

Support for the Cobalamin Deficient Population

Dietary
Food (ranked in order from 99µg/100g to 5 µg/100g): mollusks [clams, oysters (highest zinc content too!), mussels, octopus]; beef and lamb (B/L) liver and kidneys; fish eggs; fish (esp. mackerel, herring, salmon); B/L pancreas (sometimes substituted for thymus in sweet breads); B/L heart; B/L brain; giblets (chicken, turkey); crab; B/L testes; bluefin tuna; foie gras; goose and duck liver pate; sardines; emu; rabbit; beef infraspinatous (flat iron); beef gracilis (inside round cap); beef biceps femoris (bottom outside round); Beef triceps brachii (shoulder center); beef plate [brisket, skirt (fajitas), hanger]; trout; pork liver; chicken heart; lamb tongue; beef tripe; caribou; ostrich; venison; bluefish; beef chuck; B/L spleen; duck egg; cuttlefish; beef shoulder; conch; beef tenderloin; beef tongue; goose egg.

NOTES: Beef psoas major (tenderloin) and longissimus dorsi (rib eye) are among the beef cuts with the lowest Cbl content. Non-animal sources of Cbl purportedly include the seaweed Porphyra yezoensis (purple laver / nori) and the blue-green algae Spirulina platensis. Whether human Cbl requirements can actually be met by the inclusion of these foodstuffs has not yet been clarified. We therefore recommend against reliance on these "vegetarian" sources of Cbl until further information becomes available. Also be aware that cooking degrades Cbl, forming CorA. The net loss is minimally about 33% but has been found to be as high as 62%.

Augmentation
We recommend CN-Cbl if delivery is oral, buccal or sublingual; we recommend OH-Cbl if delivery is **parenteral (IM)** (CN-Cbl is acceptable parenterally if no advanced kidney pathology is present). We advise against augmenting with MeCbl or AdoCbl. We are unaware of any study demonstrating that AdoCbl or MeCbl is effective in addressing CD, SCCD, or SNCD despite the widespread, nearly 40-year use of MeCbl in pain site injections.

NOTE: OH-Cbl converts faster than CN-Cbl to Ado-Cbl and Me-Cbl and, therefore, it has a lower initial urinary excretion rate. This means that IM CN-Cbl is more likely to produce a reddish urine color even if reserves are depleted. Both OH-Cbl and CN-Cbl will have that effect once reserves have been restored. The reddish urine discoloration does not occur with oral administration as the excess is passed in the feces. In atrophic gastritis, patients show an early serologic peak in Cbl levels due to passive-diffusion-dependent absorption compared to healthy individuals.

Repletion Enhancers and Co-Factors
Hydrochloride (HCl); proteases [low pH (pepsin), neutral pH (papain, bromelain, pancreatin)], zinc (oysters 75mg/100g, peanut butter 14mg/100g, sesame butter, pumpkin seeds, & beef 10mg/100g); folate; dark green leafy vegetables (e.g. collard greens, mustard greens, kale, spinach, broccoli, arugula); calcium; magnesium; pumpkin seed oil; consuming only solid proteins and chewing until liquid; consuming a large amount of the foods listed above in one sitting on a regular basis; generously salting to taste; hydration.

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Kevin S. Millet, D.C.
Updated 9 May 2018

Total Body Modification's (TBM) Recommended Augmentation Guidelines
Standard biomedical practice for CD and SCCD is an initial oral dosage of 1000-2000mcg/day (approx. 1% of oral administered Cbl is absorbed via passive diffusion) for 1-2weeks, then 1000mcg/day for life. Customary intramuscular dosage is 100-1000mcg/day for 1-2weeks, then 100-1000mcg every 1-3 months. **Our recommendation for SNCD is sublingual CN-Cbl 5000 mcg/day for 2 weeks, 2000 mcg/day for 2 months, then 1000 mcg/day thereafter.** The portion per 1000mcg Cbl administered that is absorbed orally and parenterally is ≈13mcg (1.3%) and ≈150mcg (15%) respectively. If an adverse reaction occurs with one form of Cbl (e.g. OH-Cbl), a shift to a different preparation (e.g. CN-Cbl) may eliminate the reaction. Harmonize the form of Cbl if it tests positive on the Thymus point. We recommend against the use of "depot injections" as they are more likely to trigger an unwanted immune response. While Cbl pills and sublingual lozenges have been shown to be effective, we recommend the sublingual method of administration to maximize interspersement with salivary haptocorrin and initiate passive absorption while still in the oral cavity. For **oral augmentation** we recommend **sublingual cyanocobalamin** on an **empty stomach** or **injectable hydroxycobalamin**. **DO NOT co-ingest iron and/or vitamin C with Cbl**, as these may degrade Cbl to CorA.

NOTE: As a general rule in TBM, we strongly recommend universal substrates over biologically active substances when augmenting diet or endogenous hormones {e.g. thyroxine (T4) instead of triiodothyronine (T3), cholecalciferol (D3) not calcitriol [1,25-(OH)2D3] and pregnenalone not dehydroepiandrosterone (DHEA), estradiol (E2), progesterone, or testosterone}. This includes Cbl. A healthy body will readily determine the ratio of AdoCbl:MeCbl when OH-Cbl is consumed in animal protein in spite of any homozygous SNPs in a particular patient. In these instances, it is our experience that when proper physiologic support is provided, as is included in the Basic Physiological Exam and Autonomic Recovery Program, these so-called "impairments" are easily overcome.

For additional clinical information relating to addressing the causes and effects of cobalamin deficiency, cobalamin-related pathologies, and/or cobalamin-related genetic mutations see the 40th Anniversary edition of the Module 3 manual.

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NOTE: Items in bold are recommended additional reading. We've included a link to free pdf documents for them and others.

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