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Review Article

Cobalamin Deficiency in the Elderly

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Abstract. Older people are at risk for cobalamin (vitamin B_{12}) deficiency because of a number of common disorders (e.g., autoimmune gastritis) and drugs (e.g., antacids) that may alter its absorption and utilization. The prevalence of cobalamin deficiency increases with age, resulting, particularly elevated, in frail and institutionalized subjects. At variance with common sense, the diagnosis is far from simple. It requires a high degree of suspicion, due to heterogeneity and non-specificity of the signs and symptoms, ranging from macrocytosis (with or without anemia) to neuropsychiatric manifestations, that characterize several other aging-related disorders, like hematological malignancies, diabetes, hypothyroidism or vasculopathy. Furthermore, the detection of low levels of serum vitamin B_{12} appears poorly sensitive and specific. Other biomarkers, like serum homocysteine or methylmalonic acid, have improved the diagnostic possibilities but are expensive, not widely available, and may be influenced by some confounders (e.g., folate deficiency, or chronic renal failure). Early recognition and treatment are crucial since a proportion of patients develop severe complications, such as bone marrow failure and irreversible neurological impairment. High-dose oral treatment has proven to be as effective as the parenteral route, even in subjects with malabsorption, ensuring the complete resolution in the majority of cases. In this review, we trace the essential role of cobalamin in humans, the possible causes and impact of deficiency, the diagnostic challenges and the therapeutic options, between old and emerging concepts, with a particular focus on the elderly.

Keywords: Cobalamin; Elderly.

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Role of Cobalamin in Metabolic Processes. Vitamin B_{12}, also known as cobalamin (Cbl) is a complex water-soluble molecule, containing a cobalt atom in the center of a tetrapyrrolic ring, synthesized only by bacteria. Humans obtain Cbl from foods of animal origin, such as meat, eggs, and dairy products. Body stores, primarily located in the liver, usually contain about 2-5 mg of Cbl, with a daily turnover of less than 0.1%. Deficiency manifests when stores drop below 300 µg, a process that may take several years.[1]

Cbl is crucial for several metabolic functions, including cell proliferation and survival, energy production, and nervous system integrity, as it represents a pivotal cofactor for two[2] ubiquitously expressed enzymes, the cytosolic *methionine-synthase*, and the mitochondrial *methylmalonyl coenzyme A*

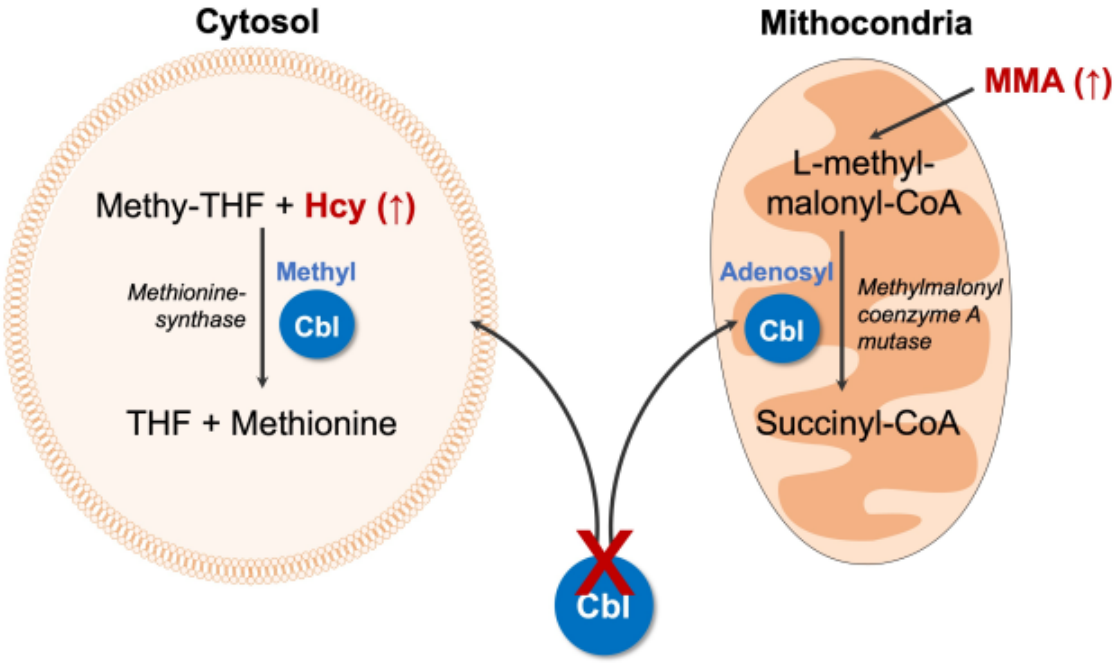

Figure 1. Intracellular biochemical pathways involving cobalamin (Cbl). In the mitochondria, Cbl is metabolized to adenosylcobalamin, a coenzyme involved in the conversion of L-methyl-malonyl-CoA to succinyl-CoA. In the cytosol, methylated Cbl acts as a coenzyme for the methionine synthase. Cbl deficiency leads to Hcy and MMA accumulation. THF: tethra-hydrofolate; Hcy: homocysteine; MMA: methylmalonic acid.

mutase (**Figure 1**).

The methionine-synthase catalyzes the conversion of methyl-tetrahydrofolate (methyl-THF) and homocysteine (Hcy) into THF and methionine, a basilar step toward DNA synthesis. The enzyme dysfunction is responsible for the nucleus-cytoplasm maturation asynchrony affecting cells with an elevated regenerative rate, predominantly the hematopoietic precursors (leading to megaloblastic anemia), but also epithelial and mucous cells (causing glossitis). Moreover, it causes a reduction of the methionine-derived metabolite S-adenosylmethionine (SAM), required for neurotransmitters and phospholipids synthesis, eventually compromising cell membrane structure and fluidity, myelin formation, and neurotransmission.[3]

The methylmalonyl coenzyme A mutase (MUT) catalyzes the isomerization of L-methyl-malonyl-CoA in succinyl-CoA, a key molecule in the tricarboxylic acid cycle, essential for ATP generation, ketone bodies metabolism, myelinization, and heme biosynthesis.

Prevalence of Cbl Deficiency (CblD) in the Elderly. Although it is known that Cbl levels tend to decline with advancing age,[4] there are little data about the true prevalence of CblD in the elderly. This is partly explained by the vast differences among subjects included in epidemiological studies, varying for age, ethnicity, food consumption (e.g., fortified or not), and comorbidities.

Further uncertainties derive from the absence of "gold standard" tests and cut-offs. Many studies, in fact, considered serum Cbl levels alone (with different standard intervals), others utilized Cbl reduction in combination with additional serum biomarkers, like homocysteine (Hcy) and/or methylmalonic acid (MMA).

Currently, the estimated prevalence of CblD ranges from 4-5% in community-living elderly[5,6] to about 30-40% in institutionalized subjects with multiple comorbidities.[7] Among the latter, CblD was responsible for anemia in 4% of cases.[8] Since the presence of anemia or macrocytosis does not accurately predict CblD,[9] some Authors have advocated generalized biochemical screening for CblD in the aged population.[9,10]

Diagnosis of CblD. The diagnosis of CblD cannot be made through a single reliable laboratory test.[11] Instead, it should be based on a thorough history, clinical manifestations, and the combined use of multiple biochemical and hematological indicators. In some cases, a trial with Cbl replacement can be very useful, with the appearance of reticulocytosis and/or improvement of neurological symptoms virtually confirming CblD.[1] Of note, peripheral blood smear is of great value as a first step in suggesting CblD and guiding differential diagnosis,[2] as it shows typical

alterations of erythrocytes and neutrophils (see below).

The *measurement of circulating Cbl* is often the first-line test to be performed. The reference intervals vary among laboratories, but, in general, levels below 150 pmol/l (200 pg/ml) are consistent with deficiency, while levels above 300 pmol/l (400 pg/ml) are considered normal. However, this test has reduced sensitivity and specificity.[1] Diagnosis may be missed in the presence of falsely normal circulating Cbl levels, as it has been observed in ordinary conditions, such as chronic liver diseases, myeloproliferative neoplasms, or in the presence of anti-intrinsic factor antibodies.[1,12] Moreover, the assay measures the two endogenous forms of Cbl, *holohaptocorrin,* and the only biologically active *holotranscobalamin* (HoloTC). A reduction in total Cbl levels may actually reflect a mere impairment of holohaptocorrin synthesis (e.g., during cancer, pregnancy, liver disease, and autoimmune disorders), with little (if any) clinical significance.

Over the past 30 years, it has become evident that *serum Hcy and MMA levels* represent more sensitive and early indicators of CblD.[1,12] Despite this, their use in clinical practice is hampered by scarce availability, the lack of validated methods and thresholds, and relatively higher costs. In addition, their levels tend to rise *per se* with aging.

In the absence of impaired renal function, an elevation of MMA (>350 nmol/l) is the most specific biomarker. The Hcy increase (>15 µmol/l) is sensitive but less specific, also rising in the case of folate deficiency, B6 vitamin deficiency, hypothyroidism, and decreased GFR. MMA and Hcy play a role in subjects with borderline Cbl values (i.e., 150-300 pmol/l), or whenever there is a discrepancy between a clinical picture suggesting CblD and apparently normal Cbl levels.[13,14] Both can be helpful in confirming a true CblD after replacement therapy, as they usually normalize within a week. MMA elevation has also been associated with poorer functional outcomes in subjects with reduced Cbl levels.[15]

Finally, the *HoloTC assay* has the best accuracy[16] theoretically, but its clinical usefulness is precluded by the scarce availability and the lack of reference values and standardization among laboratories.

Recently, a combined index of the Cbl status (named 4cB12), based on Cbl, Hcy, MMA, and HoloTc levels, has been suggested to improve the

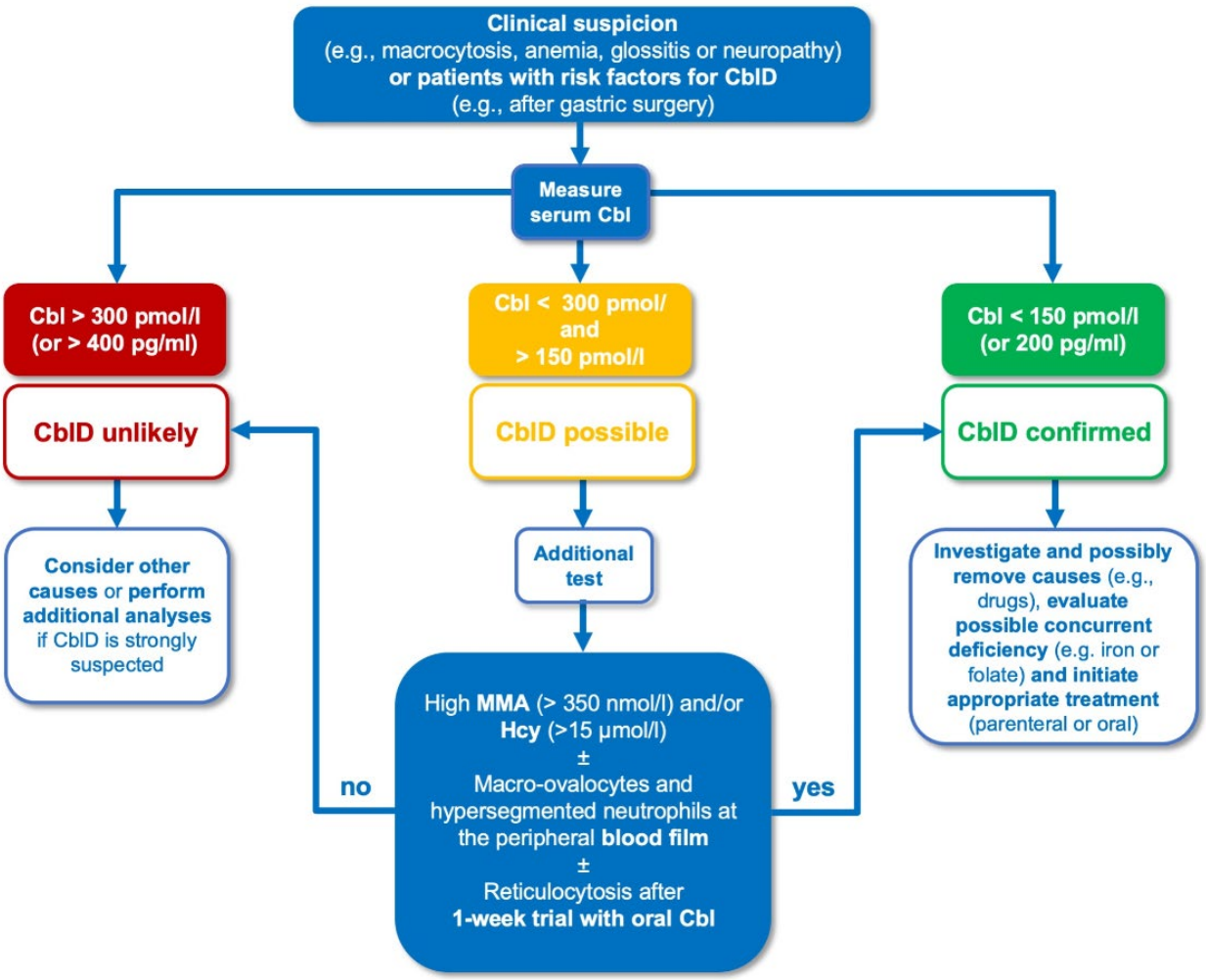

Figure 2. Possible algorithm for the diagnosis of CblD in the elderly. The diagnosis of CblD should be based on clinical signs and symptoms, and the combined use of biochemical and hematological indicators, including serum Cbl, MMA and Hcy levels, peripheral blood smear, and a trial with oral Cbl supplements.

recognition of CblD, particularly in the early subclinical stages.[17]

A possible algorithm for the diagnosis of CblD in the elderly is depicted in **Figure 2**.

Causes of CblD. Cbl in food is protein-bound, and its acquisition depends on the function of the salivary glands, gastric, and ileal mucosa.[2] Briefly, food Cbl is released in the stomach, in the presence of an adequate acid pH, through the digestive action of pepsin. Cbl then binds the salivary proteins haptocorrins (HC) and is conveyed in the small intestine, where pancreatic proteases dissociate Cbl from HC. Subsequently, Cbl forms a complex with the intrinsic factor (IF), a protein secreted by gastric parietal cells. Such complex is absorbed through a specific receptor (cubilin) expressed by enterocytes in the terminal ileum and then released to plasma, where it is bound to a family of transport proteins known as transcobalamins (TC). Finally, Cbl enters the cells through an endocytosis process mediated by TC receptors and is metabolized into adenosylcobalamin or methylcobalamin.[2]

Of note, a relatively small fraction of ingested Cbl can be absorbed along the entire intestine by passive diffusion, and that explains why high-dose oral therapy may be effective even in people with malabsorption.
Multiple conditions can interfere with the complicated multi-step journey of Cbl from food to cells. The main etiologies (summarized in **Table 1**) comprise: 1) pernicious anemia (PA), 2) maldigestion (eventually leading to the so-called "food-bound Cbl malabsorption," FBCM), 3) ileum disorders, 4) insufficient intake, and 5) increased consumption. PA and FBCM represent the primary causes in all age groups and are particularly frequent in the elderly, while an insufficient dietary intake is quite uncommon.[6] In addition to acquired causes, sporadic congenital disorders (e.g., transcobalamin deficiency) can lead to CblD, but they typically manifest in newborns and are not relevant in the elderly. On the other hand, CblD in older people is frequently multi-factorial.[12]

Pernicious Anemia. PA (considered fatal or "pernicious" before Cbl was purified in the liver, in 1948) is a common cause of CblD worldwide.[6] It is particularly relevant in people older than 60 years, in whom the estimated prevalence ranges from 2 to 12%, and increases with aging.[18]

The disorder is a consequence of severe immune-mediated damage of the gastric mucosa, which causes atrophy (atrophic autoimmune gastritis, AAG), especially in the fundus and the body, with a spared antrum. Histological confirmation of gastric atrophy

Table 1. Main causes for Cbl deficiency in the elderly.

Pernicious anemia (autoimmune atrophic gastritis)
Food-bound Cbl malabsorption
Hp-related atrophic gastritis
Bacterial overgrowth
Chronic alcoholism
Pancreatic exocrine insufficiency
Sjogren syndrome
Ingestion of antacids, metformin, cholestyramine, colchicine
Total or partial gastric resection
Gastric bypass or other bariatric surgery
Malabsorption due to disorders of ileum mucosa
Crohn's disease
Radiation enteritis
Tropical sprue
Celiac disease
Lymphoma
Tuberculous ileitis
Fish tapeworm infestation, giardiasis
Amyloidosis
Ileal resection (>20-30 cm)
Poor dietary intake
Malnutrition
Chronic alcoholism
Vegetarian or vegan diet (or diet with low intake of meat or dairy products)
Increased Cbl consumption (high tissue turnover)
Chronic hemolysis
Ineffective erythropoiesis
Cancer
Hyperthyroidism

needs for PA diagnosis. In addition, diagnosis is confirmed by the presence of two types of auto-antibodies, targeting the acid-producing H+/K+ ATPase of parietal cells (Parietal Cells Antibody or PCA), or the IF/IF binding site in the small bowel (Intrinsic Factors Antibody or IF), respectively.[18] PCA causes hypo- or achlorhydria through the destruction of the parietal cells, also impairing the production of IF. Their presence may precede clinically overt atrophic gastritis by several years. PCA has high sensitivity (80-90%) in the early stage of the disease, but much lower specificity (50%), since they are also present in other autoimmune diseases (e.g., thyroiditis, type 1 diabetes, Addison's disease, and vitiligo), as well as in healthy elderly without AAG.[18] IFA, which hamper the Cbl-IF complex formation or its binding to enterocytes, are considered more specific markers but have lower sensitivity (around 60%).[18]

Fasting hypergastrinemia (present in 75% of subjects) and low Pepsinogen I levels may be useful in the diagnosis of PA,[19] while the *Shilling test* that specifically investigated IF-mediated malabsorption has been abandoned due to its complexity and the need of using of isotope-labeled Cbl.

The diagnostic workup should also include an evaluation of iron status. Indeed, achlorhydria causes iron malabsorption and may lead to iron deficiency (ID) that typically precede megaloblastic anemia. PCA and endoscopic atrophic gastritis are encountered in about 20-30% of patients with unexplained or refractory ID.[20]

Moreover, screening for autoimmunity is indicated,[21] as a proportion of patients (especially those with genetic susceptibility associated with specific HLA-DR pattern) may develop other organ-specific immune-mediated disorders. Recent studies demonstrated that thyroid disorders (particularly Hashimoto's thyroiditis) affect up to 40% of patients with AAG and may be asymptomatic in the majority, leading to diagnostic and treatment delays.[22] Thyroiditis with AAG (formerly known as "thyrogastric syndrome") is currently considered part of the polyglandular autoimmune syndromes, which include several endocrine and nonendocrine manifestations.[23]

Finally, patients with PA harbor almost 7-fold higher risk of developing gastric neoplasms (adenocarcinomas, lymphomas, and carcinoids)[24] as an end-stage evolution of gastric atrophy, achlorhydria and compensatory hypergastrinemia, which causes cellular metaplasia. For this reason, many experts recommend that adults with PA undergo endoscopic surveillance at baseline and every 3 to 5 years for life, although this practice is not universally accepted.[25]

Food-bound cobalamin malabsorption. FCBM syndrome is characterized by the inability to release Cbl from food or intestinal binding-proteins, generally as a consequence of achlorhydria, in the presence of normal ileal mucosa.[6] Despite the name, more appropriately, this entity refers to conditions characterized by inadequate digestion, i.e., caused by non-immune atrophic gastritis (e.g., *Helicobacter pylori*-related gastritis), intestinal bacterial overgrowth,[26] chronic alcoholism, pancreatic exocrine insufficiency, Sjogren's syndrome. Multiple drugs can also determine FCBM, such as long-term ingestion of proton pump inhibitors (PPI), antacids, H_2-receptor antagonists (H2-RA), and metformin. FBCM typically produces a slow, progressive depletion of Cbl. Clinical manifestations tend to be subtle, although progression to more severe forms can still occur in a minority of patients.

H. pylori-related gastritis. The most relevant form of FBCM is caused by chronic *H. pylori* (HP) infection, a common disorder in aged people.[27] HP is strongly associated with atrophic gastritis. The mechanisms by which HP provokes gastritis are still unclear, but the production of antibodies cross-reacting with parietal cells H+/K+ ATPase may be involved. Interestingly, HP eradication has been reported to improve not only anemia and mean corpuscular volume (MCV), but also Cbl levels.[28] The same was not observed in subjects in whom eradication therapy was unsuccessful. In successful cases, the positive Cbl balance may be related not only to HP eradication *per se* but also to the eradication of other small intestine bacteria potentially interfering with Cbl uptake.[26] Treating HP is also important to reduce the risk of gastric cancer, which is increased in patients with long-standing infection.[29,30]

Drugs. In the elderly, long-term polypharmacy for comorbidities may favor CblD.[31] PPI and H2-RA suppress both gastric acid secretion and IF production. A study including >200,000 subjects showed that CblD was more common in people assuming PPI or H2-RA for >2-years, especially in those treated with the highest dose.[32] Similarly, a recent systematic review and meta-analysis[33] were consistent with a higher risk of CblD in people chronically using PPI.

Metformin interferes with the Cbl absorption via a dose-dependent reduction of intestinal free calcium ions required for uptake of the Cbl-IF complex by ileal enterocyte receptors.[34]

Although PPI, H2-RA, and metformin appear to reduce Cbl bioavailability, the clinical significance of such an effect is still controversial. In clinical practice, it is crucial to keep in mind this as an additional cofactor in subjects with other predisposing factors (e.g., in those with high Cbl need due to chronic hemolysis), as well as in those with anemia and neurologic/cognitive impairments. Anyway, a regular reassessment of actual benefits and risks associated

with these drugs is recommended, especially in the elderly.

Gastric surgery. Total or partial gastrectomy are relatively common causes of CblD. Achlorhydria and the absence of pepsin lead to impaired Cbl dissociation from food, and the reduced IF production impairs Cbl absorption. In patients with total gastrectomy, CblD occurs relatively early (after about 15 months), while in partial distal resections presentation is delayed by several years, mainly in patients with low pre-operative Cbl stores.[35] Cbl supplementation is always required after gastric surgery.

Malabsorption Due to Small Intestine Disorders. Several disorders of the small intestine have the potential to interfere with Cbl absorption, especially if the ileum is involved. These conditions include inflammatory bowel disease (IBD), radiation enteritis, tropical sprue, celiac disease, lymphoma, tuberculous ileitis, *Diphillobotrium latum* infestation (deriving from the ingestion of raw freshwater fish[36]), amyloidosis, and ileal resection (especially greater than 20-30 cm).[38] Cbl levels should be periodically monitored (e.g., every six months) in these conditions.

Dietary Poor Intake. A typical Western diet provides around 5-30 μg daily of Cbl, 15-20% of which is absorbed. This amount is higher than the Recommended Daily Allowance (RDA), varying among different regions from 1 μg (Europe) to 2.4-2.8 μg (USA). Therefore, CblD is rarely attributable to pure nutritional deficiency, even in the elderly.[6] However, a clinically relevant CblD can develop during very restrictive diets that exclude animal-source foods, such as in vegans, or less frequently, in vegetarians.[39,40] In these subjects, routine Cbl supplements should be recommended. Physicians should be aware that some individuals may be reluctant to take supplements due to misconceptions and aversion to artificially manipulated food products.[40]

Increased Cbl Consumption. Elevated Cbl consumption may characterize conditions with increased cell turnover, such as chronic hemolytic disorders with erythropoiesis expansion, neoplasms, and hyperthyroidism.

Clinical Manifestations . The clinical manifestations of CblD are insidious and heterogeneous, with some subjects being more prone to hematological disorders and others developing preferentially severe neurological impairments in the absence of anemia and/or macrocytosis. Many cases of CblD are overlooked for years and sometimes even misdiagnosed, possibly leading to irreversible sequelae. Non-specific symptoms include asthenia, diarrhea, inappetence, lethargy, poor memory. The typical CblD features are megaloblastic anemia (MA) and neurological disorders.

Megaloblastic Anemia. The first description of MA dates back to the mid-1800s in a patient with concomitant myeloneuropathy and glossitis. MA defines a condition characterized by the presence of macro-ovalocytes in the peripheral blood, associated with megaloblasts (i.e., abnormal erythroblasts with elements larger than average and asynchronous

Table 2. Differential diagnosis of macrocytosis (with or without anemia) in the elderly.

Causes	Clinical and laboratory evaluation
Cbl deficiency	Serum Cbl (<150 pmol/), Hcy (>15 μmol/) and/or MMA (>30 nmol/l) Reticulocytes (↓) ± PCA, IFA, Hp fecal antigen Macro-ovalocytes and neutrophil hypersegmentation at peripheral blood smear
Folate deficiency	Serum folates (↓) Reticulocytes (↓)
Liver diseases/cirrhosis	Consider risk factors for liver disease Transaminases (↑) Albumin (↓), PT (↑), polyclonal hypergammaglobulinemia
Alcohol abuse	Evaluate daily alcohol intake Transaminases (↑ AST>ALT), γGT (↑) Carbohydrate Deficient Transferrin (CDT) (↑)
Conditions associated with reticulocytosis	Consider possible chronic hemolysis*, acute bleeding or ESAs treatment Reticulocytes (↑) *Aptoglobin (↓), LHD (↑), bilirubin (↑)
Drugs	Ask about treatments with methotrexate, hydroxyurea, alkylating agents, purine and pyrimidine inhibitors, imatinib, anticonvulsants, antiretroviral therapies for HIV infection
Myelodysplastic syndrome	Reticulocytes (↓) Presence of unexplained cytopenia (even bi- or tri-linear) Bone marrow examination
Hypothyroidism	TSH (↓ or ↑), fT4 (↓)

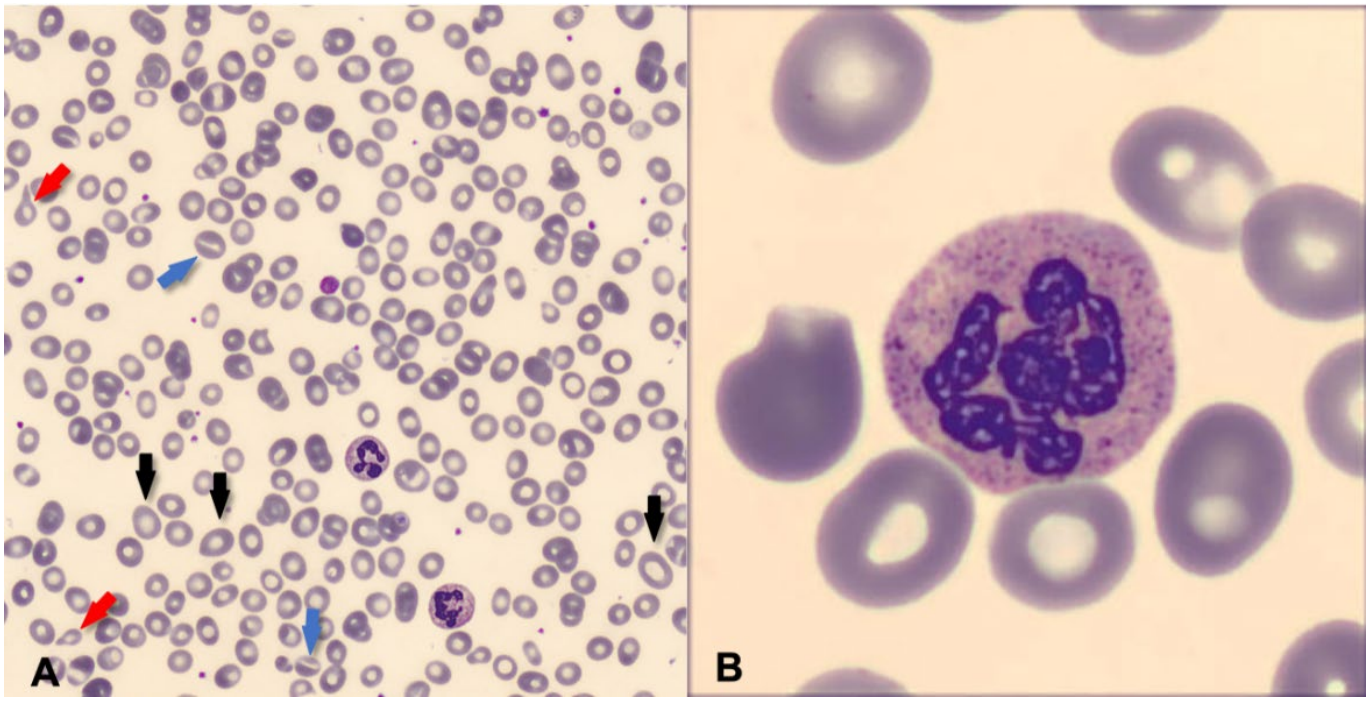

Figure 3. Peripheral blood smear in an elderly woman affected by pernicious anemia, showing macro-ovalocytes (black arrows), anisopoikilocytosis, sparse dacriocytes (red arrows), and stomatocytes (blue arrow) (**A**); neutrophil hypersegmentation of the nucleus (**B**). Complete Blood Count (CBC): Hb 6.4 g/dl, MCV 107.7 fl, MCH 38.1 pg, RDW 20.9%, leukocytes 5.38 x 10^9/µl, platelets 128,000/µl.

nucleus-cytoplasm maturation) at variable proportion in the bone marrow, which confer the typical "blue" appearance.[2] The anemia is macrocytic (MCV 100-150 fl or more), while isolated macrocytosis and anisocytosis (increased red cell distribution width, RDW) may precede anemia by several months. MA is slowly progressive and, as such, generally well-tolerated, so that very low Hb values (5-6 g/dl) are often detected at diagnosis. Of note, increased MCV may be poorly informative in the elderly, in whom ID (with opposite effect on MCV) is highly prevalent.[41] **Table 2** summarizes the main causes of macrocytic anemia in the elderly.

In addition to ineffective erythropoiesis, the erythrocytes released into the circulation have increased rigidity, which may be responsible for peripheral hemolysis, leading to haptoglobin consumption and elevation of both serum bilirubin and lactate dehydrogenase (LDH). The peripheral blood smear may show anisocytosis, poikilocytosis, stomatocytes, dacriocytes, red cell fragments, and target cells (**Figure 3A**). Thrombocytopenia and leukopenia may also occur. Neutrophils typically present hypersegmentation of their nuclei[2] (**Figure 3B**). Detection of at least 3 neutrophils with at least 5 lobes, or one containing at least 6, is considered specific for CblD. Hypersegmented neutrophils are an early sign of megaloblastosis, but they have scarce sensitivity and may persist for days after Cbl levels correction. In severe cases, the initial differential diagnosis can include myelodysplastic syndromes, hemolytic anemias, or even acute leukemia. Severe CblD could lead to a picture that mimics thrombotic microangiopathy (TMA),[42] also known as pseudo-TMA. Both conditions are characterized by red cell fragmentation coupled with thrombocytopenia. An evaluation of reticulocytes count (reduced in severe CblD, elevated in TMA) is generally useful for differentiating the disorders[43] and is critical to avoid unnecessary/complex treatment for TMA.[44]

Neuropsychiatric Impairment. CblD has been associated with a broad spectrum of neurologic, cognitive, and psychiatric manifestations.[45] Of note, it could contribute to reducing responsivity to antidepressants.[46]

Recognizing CblD as the etiology of neuropsychiatric signs in the elderly requires a high degree of suspicion, since they may develop before or even in the absence of anemia or macrocytosis in around 20% of patients.[36,47] Neurological impairment is usually heralded by proprioception and vibration loss due to peripheral sensory neuropathy. Other common neurological findings include paresthesia, gait ataxia, abnormal reflexes, bowel/bladder incontinence, optic atrophy, altered smell and taste, lethargy, and extrapyramidal signs. Autonomic dysfunction can also occur, leading to orthostatic hypotension and syncope.[45] CblD in the elderly can be associated with poor coordination, walking difficulties, falls, and loss of function.

Subacute combined degeneration (SCD) of the spinal cord due to demyelination is a rare complication of CblD, which, if untreated, may cause irreversible

spastic ataxia. SCD can be detected by MRI in T2-weighted images, showing symmetrical hyperintensity of posterior and lateral columns in the cervical and thoracic spinal cord, although imaging sensitivity appears quite low.[48]

In advanced stages, cognitive decline, psychosis with hallucinations,[45] and depression[49] may be observed. Severe CblD in the elderly may predispose to delirium,[45,50,51] although this association has been confuted by a recent report.[52]

Of note, recent trials do not support Cbl supplementation in the elderly with normal to low Cbl levels for preventing cognitive deterioration.[53,54]

Other Manifestations. CblD may lead to epithelial changes, including glossitis, angular stomatitis, skin hyperpigmentation, dermatitis, nail, and hair abnormalities.[55]

Low Cbl levels, with or without hyperhomocysteinemia, has been associated with high markers of bone turnover and increased fracture risk.[56] However, the clinical relevance of such association is debated, and, at present, supplementation cannot be recommended for preventing fracture in the elderly.[57,58]

Finally, hyperhomocysteinemia resulting from CblD has been associated with endothelial dysfunction,[59] and accelerated atherosclerosis.[60,61] However, studies evaluating Hcy-lowering treatment by B-vitamins supplementation have failed to demonstrate an improvement in cardiovascular outcomes.[62,63]

Treatment. In many patients, the causes of CblD cannot be removed, and lifelong Cbl replacement therapy is required. CblD occurs over months or years, and usually, there is no need for urgent action. However, in some circumstances, it may be warranted to correct CblD rapidly, as in the case of neurologic symptoms, due to the risk of irreversible sequelae, or in severe/symptomatic anemia. Special considerations should be made for the elderly, who often take many medications and may be poorly compliant with oral therapy.[64,65]

Cbl can be administered orally and parenterally (intramuscularly, IM). Subcutaneous, transdermal, sublingual, and nasal formulations are also available, but their role in clinical practice appears marginal, because of their variable effectiveness and higher costs.[65] Two formulations are currently available, cyanocobalamin and hydroxocobalamin.

Initial parenteral administration is appropriated in the subjects with (e.g., PA, or gastric resections) and in those with symptoms, requiring a prompt correction.[45,64] The typical schedule consists of 1 injection (1,000 mg, of which about 10% is retained) three times a week for 1 to 2 weeks, followed by weekly injections for a month. Maintenance therapy is based on monthly administration for cyanocobalamin, once every other month, for hydroxocobalamin.

Oral Cbl (50-150 μg/day) represents a cheaper and easier route of administration, more comfortable for the patients and effective in the majority of mild-moderate cases.[66] It is also more suitable in patients under anticoagulant therapy, in whom IM injections may be contraindicated. Recently, its role has been re-evaluated even in subjects with malabsorption or FBCM, in which high-dose oral Cbl (1,000 μg daily) has proven as non-inferior to the parenteral route.[67,68] Indeed, small amounts of Cbl (0.5-4%) can be passively absorbed by the entire bowel, via an IF-independent pathway.[69] Therefore, high oral doses of 1,000 μg deliver at least 5 μg of Cbl, which are largely sufficient to satisfy daily requirements. However, in clinical practice, the role of high-dose oral Cbl in PA or malabsorption is still debated, and injectable Cbl remains frontline therapy. Food alters oral Cbl absorption; thus, it should preferably be assumed on an empty stomach.

Monitoring the hematological and clinical response to Cbl replacement therapy is essential, as it is useful to confirm the diagnosis. Typically, the reticulocyte crisis occurs in 1 week, anemia and macrocytosis improve within 3-4 weeks, and normalization of Hb and MCV is generally achieved within sixth-eighth weeks. The neurological response is less predictable and can take from 1 week to 3 months.[64] Neurological irreversible damages have been described in about 6% of cases, and are more frequent in patients with ≥6-months treatment delay.[36]

Monitoring serum Cbl levels is scantly informative since they rapidly rise with supplementation regardless of the actual repletion of Cbl body stores. Serum MMA and Hcy levels tend to decrease or even normalize by the first week (unless renal failure coexists), and this may further support the diagnosis in uncertain cases.[64]

Particular attention has to be paid to other possible causes of anemia, such as folate and iron deficiency. In patients with both Cbl and folate deficiency, Cbl should be given first in order to avoid the risk of precipitating SCD of the spinal cord.[36]

Moreover, some drugs may interfere with Cbl metabolism and absorption. This is particularly true for PPI, which are often inappropriately prescribed in the elderly,[37] and whose cessation should be considered whenever clear indications for their use are not present.

Cbl supplements are generally well-tolerated even when prescribed at high doses. Adverse effects may include hot flushes, acneiform eruptions,[70] and, quite rarely, severe allergic reactions (i.e., anaphylaxis), especially in subjects with cobalt sensitivity.[36,55] Transient hypokalemia can be observed when severe anemias respond to Cbl as a consequence of potassium uptake by growing hematopoietic cells, but its clinical relevance has never been proven.[1]

Concerns have been raised about the safety of

generalized Cbl supplementation, especially regarding a possible increased risk of lung cancer.[71,72,73] However, a meta-analysis of randomized controlled trials (RCTs) denied any effects of Cbl supplementation on cancer incidence or mortality, rather showing a lower risk of melanoma.[74] Monitoring circulating Cbl levels in lifelong treated high-risk patients (e.g., male smokers) could be a reasonable approach to avoid overtreatment.

Finally, the use of multivitamin supplements is becoming very popular among older people. Taking these supplements, which often contain low-dose Cbl (3-5 µg/day) in association with vitamin D, iron, or proteins, may be theoretically useful for short periods, for instance, to compensate poor nutrition after a disabling disease. However, there is currently no evidence of their efficacy in preventing CblD, and probably they have little (if any) effects in treating CblD in the elderly.

Conclusions. CblD is relatively common in the elderly, but often underrecognized because of non-specificity and heterogeneity of clinical manifestations, as well as the lack of reliable laboratory tests. Increasing clinicians' awareness is essential to avoid misdiagnosis. Further research is needed to identify better biomarkers of CblD, to define the relevance of subclinical CblD in the elderly, as well as the usefulness of screening programs and the long-term safety of Cbl supplements, including novel nasal or sublingual formulations.

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