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Inherited Disorders of Cobalamin Metabolism: A Practical Guide for the Internist

Emmanuel Andrès*, Jean-Edouard Terrade, Xavier Jannot and Noel Lorenzo-Villalba

Department of Internal Medicine, Hôpitaux Universitaires de Strasbourg (HUS); EA 3072, University of Strasbourg (UdS); Strasbourg, France

ABSTRACT

Inherited disorders of cobalamin (vitamin B12) metabolism (IDCM) constitute a clinically heterogeneous group of inborn errors of intermediary metabolism resulting from defects in intestinal absorption, plasma transport, or intracellular processing of this essential cofactor. Long regarded as exclusively pediatric diseases, late-onset and adult-presenting forms — notably late-onset cblC disease (biallelic MMACHC variants) and remethylation cycle disorders — are increasingly recognized in internal medicine. In adults, the clinical spectrum encompasses unexplained neuropsychiatric syndromes, recurrent thromboembolic events, chronic kidney disease, and atypical hematological findings, frequently in the presence of normal serum vitamin B12 concentrations, creating a persistent diagnostic gap.

Plasma total homocysteine, often markedly elevated and accompanied by elevation of methylmalonic acid, is the most sensitive initial biochemical marker, enabling localization of the defect prior to confirmation by multigene sequencing. Parenteral hydroxocobalamin, superior to cyanocobalamin for intracellular utilization, combined with betaine and folinic acid (vitamin B9) supplementation, can halt disease progression and partially reverse neurological injury when initiated early. In refractory or cobalamin-unresponsive forms, liver transplantation reduces systemic metabolic burden, while gene and mRNA therapies constitute emerging disease-modifying strategies.

*Corresponding author

Emmanuel Andrès, Service de Médecine Interne, Hôpital de Hautepierre, Hôpitaux Universitaires de Strasbourg (HUS), 1, Avenue Molière, 67091 Strasbourg, France.

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Key Messages for The Internist

- An inherited disorder of cobalamin (vitamin B12) metabolism (IDCM) should be suspected in adults presenting with unexplained neuropsychiatric syndromes, recurrent thromboembolic events, renal impairment, or atypical hematological findings — even when serum cobalamin concentrations are within normal limits.
- Plasma total homocysteine (tHcy) and methylmalonic acid (MMA) — plasma or urinary — are the pivotal first-line investigations; their combination directs the diagnosis towards the specific metabolic defect.
- Parenteral hydroxocobalamin is the treatment of choice in cobalamin-responsive forms; betaine, folinic acid (vitamin B9), and carnitine constitute the essential adjunctive therapies.
- Delayed diagnosis leads to irreversible neurological sequelae, progressive chronic kidney disease, and recurrent vascular events; early treatment can stabilize or partially reverse multisystem complications.

In cobalamin-unresponsive forms, liver or combined liver–kidney transplantation reduces metabolic burden; gene therapy and mRNA-based approaches represent imminent therapeutic prospects.

Introduction

Vitamin B12 (cobalamin), isolated in 1948 as the curative factor for pernicious anemia (also named Biermer's disease), is an essential water-soluble cofactor required for two fundamental enzymatic reactions: the cytosolic remethylation of homocysteine to methionine by methionine synthase (dependent on methylcobalamin), and the mitochondrial isomerisation of methylmalonyl-CoA to succinyl-CoA by methylmalonyl-CoA mutase (dependent on adenosylcobalamin) [1].

Inherited defects disrupting any step of these pathways generate characteristic metabolic signatures — methylmalonic acidemia, hyperhomocysteinaemia, or both - which constitute the biochemical key to diagnosis. Although historically encountered almost exclusively in pediatric practice, late-onset and adult presentations are now increasingly recognized, driven by advances in metabolomics, next-generation sequencing, and the growing cohort of patients diagnosed in the neonatal or early pediatric period who are transitioning to adult care [2-4].

The diagnostic challenge for the internist is threefold: major phenotypic heterogeneity; normal or near-normal serum cobalamin concentrations in intracellular processing defects (a discordance that can misdirect clinicians towards alternative diagnoses for months to years); and the intrinsic rarity of these conditions, which leads to limited physician familiarity.

This review provides internists and adult medicine specialists with an evidence-based synthesis of the biochemistry, classification, multisystem clinical manifestations, diagnostic strategy, and current and emerging treatments, with particular emphasis on differential diagnosis and adult-onset presentations [5-7].

Biochemistry and Intracellular Cobalamin Processing

Dietary cobalamin is released from food proteins by gastric acid and pepsin, then transferred sequentially through haptocorrin (gastric R-binder), intrinsic factor (secreted by gastric parietal cells), and the ileal cubam receptor complex (cubilin–amnionless) into enterocytes [8,9]. In the portal circulation, cobalamin is bound to transcobalamin II (TCN2), which delivers it to virtually all nucleated cells via the CD320 receptor. Following receptor-mediated endocytosis and lysosomal degradation of the transcobalamin–cobalamin complex, free cobalamin is exported into the cytosol via LMBRD1 (cblF) and ABCD4 (cblJ) [10,11].

Within the cytosol, MMACHC catalyzes reductive decyanation or dealkylation of incoming cobalamin species, generating cob (II) alamin - a central intermediate from which the vitamin is directed towards one of two metabolically active cofactor forms [12]. Methylcobalamin is synthesized via the MTR/MTRR pathway and supports methionine synthase–mediated remethylation of

homocysteine using 5-methyltetrahydrofolate as the methyl donor. Adenosylcobalamin is generated in mitochondria after MMADHC-mediated trafficking and MMAB (adenosyltransferase) activity, serving as cofactor for methylmalonyl-CoA mutase [13].

Defects proximal to the metabolic branch point result in combined methylmalonic acidemia and hyperhomocysteinaemia, whereas lesions affecting only one downstream pathway produce isolated biochemical phenotypes - a distinction that underpins the diagnostic algorithm presented below [6-14].

Classification of Inherited Cobalamin Disorders

Inherited cobalamin disorders are classified according to the affected step: defects of intestinal absorption and plasma transport, and defects of intracellular cobalamin processing, further subdivided by somatic cell complementation groups (cblA–cblJ and related entities) [14,15]. The most frequent and clinically relevant disorder for the adult internist is cblC disease (MMACHC), with an estimated incidence of 1:100,000–1:200,000 live births. Early-onset cblC disease (approximately 90% of cases) presents within the first months of life with severe multisystem involvement; late-onset cblC disease presents from adolescence onward with a heterogeneous phenotype that frequently mimics acquired nutritional deficiency [2,3,6].

Table 1: Classification and Key Features of Inherited Cobalamin Disorders

Disorder / Group	Gene(s)	Biochemical signature	Cobalamin responsiveness	Primary presentation in adults
Intrinsic factor deficiency	GIF	↓ serum B12, ↑ MCV	Yes (parenteral)	Megaloblastic anemia (rare in adults unless previously undiagnosed)
Imerslund–Gräsbeck syndrome	CUBN / AMN	↓ serum B12, proteinuria	Yes (parenteral)	Anemia + proteinuria; diagnosis often delayed into adulthood
Transcobalamin II deficiency	TCN2	Normal serum B12; ↓ holotranscobalamin; pancytopenia	Yes (high-dose parenteral)	Rare; immunodeficiency, pancytopenia in infancy → adult survivors
cblC disease (MMACHC)	MMACHC	↑↑ MMA + ↑↑ tHcy	Partial	Neuropsychiatric syndrome, TMA, nephropathy, thrombosis — late-onset form predominant +++
cblD (MMADHC)	MMADHC	↑ MMA ± ↑ tHcy	Variable	Neurological, hematological
cblA (MMAA)	MMAA	↑ MMA; normal tHcy	Yes	Metabolic crises, CKD
cblB (MMAB)	MMAB	↑ MMA; normal tHcy	No	Metabolic crises, severe CKD
cblE (MTRR) / cblG (MTR)	MTRR / MTR	↑ tHcy; normal MMA	Partial	Neurological, psychiatric, thrombosis
cblF (LMBRD1)	LMBRD1	↑ MMA + ↑ tHcy	Yes	Rare; variable multisystem
cblJ (ABCD4)	ABCD4	↑ MMA + ↑ tHcy	Yes	Rare; variable multisystem
Isolated MMA (mutase, mut ^o /mut ⁻)	MMUT	↑↑↑ MMA; normal tHcy	No	CKD, metabolic crises, neurological

CKD = Chronic Kidney Disease; MMA = Methylmalonic Acid; tHcy = Total Plasma Homocysteine; TMA = Thrombotic Microangiopathy. References: [1-21]

Clinical Manifestations in Adults: The Internist’s Perspectives

Inherited cobalamin disorders present in adults as multisystem diseases with highly variable expressivity. The clinical picture is shaped by the underlying biochemical defect, its functional consequences (impaired methylation, methylmalonic acid accumulation, or both), and the duration of diagnostic delay. Awareness of the breadth of possible presentations is essential for the internist to prevent the years of diagnostic wandering documented in published cohorts [2,3,6].

Table 2: Systemic Clinical Manifestations of Inherited Cobalamin Disorders Relevant to Adult Medicine

System	Key manifestations in adults	Biochemical context	Most associated disorders
Neurological	Subacute combined degeneration of the spinal cord (posterior + lateral columns), spastic paraparesis, sensory ataxia, peripheral neuropathy, progressive cognitive decline, dementia	↑MMA + ↑tHcy or isolated remethylation defect	cblC (late-onset), cblE, cblG, cblD
Psychiatric	Refractory depression, psychosis, behavioral change, acute confusional state, obsessive–compulsive disorder	Remethylation defect, hyperhomocysteinaemia	cblC (late-onset), cblE, cblG
Thromboembolic / vascular	Recurrent DVT/PE, ischemic stroke in young adults, arterial thrombosis, TMA (aHUS-like), pulmonary arterial hypertension	Severe hyperhomocysteinaemia, endotheliopathy	cblC, cblE, cblG, cblD
Renal	Chronic tubulointerstitial nephropathy, glomerular proteinuria, acute renal TMA (aHUS-like syndrome), progressive CKD requiring dialysis	cblC (especially c.80A>G variant), complement dysregulation	cblC, Imerslund–Gräsbeck syndrome
Hematological	Megaloblastic anemia, macrocytosis, hyper-segmented neutrophils, pancytopenia. IMPORTANT: often absent or subtle in intracellular processing defects!	Methylcobalamin / methionine synthase pathway defect	cblC, cblE, cblG, TCN2 deficiency
Ophthalmological	Pigmentary maculopathy (hallmark of cblC), progressive visual loss, nystagmus, strabismus (severe early-onset forms)	↑MMA + ↑tHcy	cblC (characteristic), cblD
Cardiovascular	Dilated cardiomyopathy, pulmonary arterial hypertension, accelerated atherosclerosis, non-bacterial thrombotic endocarditis (very rare)	Systemic metabolic derangement, Hcy toxicity	Severe cblC, remethylation defects
Hepatic	Hepatomegaly, elevated transaminases and GGT, hepatic steatosis (less common in adults)	Mitochondrial dysfunction	Severe cblC forms, isolated methylmalonic acidemia
Dermatological / appendages	Glossitis, angular cheilitis, cutaneous hyperpigmentation, brittle hair (correlated with functional cobalamin status and hyperhomocysteinaemia)	Global functional cobalamin deficiency	Absorption and transport defects

CKD = Chronic Kidney Disease; DVT/PE = Deep Vein Thrombosis/Pulmonary Embolism; Hcy = Homocysteine; MMA = Methylmalonic Acid; TMA = Thrombotic Microangiopathy; aHUS = Atypical Hemolytic Uremic Syndrome. References: [2,3,5,6,14,17].

Neurological Manifestations

Neurological disease is the dominant determinant of long-term morbidity in adults. The classic presentation of late-onset cblC disease mimics subacute combined degeneration of the spinal cord -posterior and lateral column dysfunction with sensory ataxia, spastic paraparesis, and loss of vibration sense- clinically indistinguishable from nutritional cobalamin deficiency unless comprehensive biochemical profiling is requested [2,3]. Peripheral neuropathy, motor dysfunction, and progressive cognitive decline are also well documented.

The pathophysiology is multifactorial: impaired S-adenosylmethionine-dependent methylation of myelin basic protein, direct neurotoxicity of homocysteine and methylmalonic acid (MMA), mitochondrial dysfunction, and oxidative stress [2-6]. Brain MRI may reveal white matter hyperintensities (FLAIR), diffuse cortical atrophy, or posterior column spinal cord signal changes - findings that, in unrecognized cases, may prompt consideration of leuco-dystrophy or multiple sclerosis.

Psychiatric Manifestations

Psychiatric involvement is increasingly recognized in late-onset remethylation disorders and may antedate overt neurological signs

by months to years, contributing to systematic misattribution of symptoms to primary psychiatric diagnoses. The spectrum includes mood disorders (notably depression), behavioral changes, cognitive deterioration, acute confusional states, and frank psychosis [2,3,22].

Disruption of monoamine neurotransmitter pathways (dependent on methionine-derived S-adenosylmethionine), white matter dysfunction, and impaired one-carbon metabolism collectively underlie these manifestations. Adult physicians encountering young patients with treatment-refractory psychiatric presentations should include plasma homocysteine measurement as a first-line screen.

Thromboembolic and Cardiovascular Manifestations

Thromboembolic events - venous thrombosis, arterial thrombosis, cerebrovascular events, and microangiopathic processes - represent a recognized and potentially life-threatening complication, particularly in remethylation disorders associated with markedly elevated homocysteine. Endothelial dysfunction, impaired nitric oxide signaling, and a prothrombotic hemostatic profile driven by hyperhomocysteinaemia collectively increase vascular risk.

Cardiovascular manifestations include cardiomyopathy in severe early-onset disease, pulmonary arterial hypertension in selected cases, and diffuse atherosclerotic disease in chronic hyperhomocysteinaemia. In young adults presenting with ischemic stroke or recurrent DVT without conventional risk factors, systematic measurement of plasma total homocysteine (tHcy) and MMA is mandatory.

Renal Manifestations

Renal involvement ranges from chronic tubulointerstitial nephropathy and proteinuria (especially in Imerslund - Gräsbeck syndrome and cblC disease) to acute thrombotic microangiopathy resembling atypical hemolytic uremic syndrome (aHUS), most pronounced in cblC disease with the c.80A>G variant [5-23]. Endothelial injury driven by hyperhomocysteinaemia, oxidative stress, and complement dysregulation has been implicated. Renal dysfunction may progress despite treatment and occasionally requires renal replacement therapy or transplantation [24,25].

Practical Point for the Internist

Any presentation of aHUS in a young or middle-aged adult, particularly when associated with neurological or hematological abnormalities, should prompt measurement of plasma MMA and tHcy before initiating eculizumab therapy, so as not to miss a treatable underlying IDCM.

Hematological Manifestations

Megaloblastic anemia with macrocytosis, hyper-segmented neutrophils, and variable pancytopenia is common, particularly in disorders affecting methylcobalamin-dependent methionine

synthase activity. These abnormalities reflect functional folate trapping within the one-carbon metabolism pathway, with consequent impairment of thymidylate and purine synthesis [21,26].

Critical Point for the Adult Clinician

A normal mean corpuscular volume and normal serum cobalamin concentration do not exclude an inherited cobalamin disorder. In intracellular processing defects, hematological markers are frequently unimpressive or entirely absent at presentation. Plasma MMA and tHcy should be measured even when the full blood count is normal in the appropriate clinical context.

Ophthalmological Manifestations

Pigmentary maculopathy with progressive visual impairment is a hallmark of cblC disease and may persist or progress despite biochemical control [2-4]. Fundoscopic examination and Optical Coherence Tomography (OCT) should be incorporated into the initial evaluation of all adults diagnosed with cblC or related disorders, and repeated annually during follow-up.

Biological Abnormalities: A Structured Approach for the Internist

The biochemical diagnosis of IDCMs rests on a stepwise strategy, proceeding from the most accessible to the most specialized investigations. Isolated serum cobalamin measurement is insufficient — and misleading — to exclude an IDCM. Table 3 summarizes the essential biochemical parameters, their diagnostic value, and their practical interpretation [10,26,27].

Table 3: Biological Abnormalities in Inherited Cobalamin Disorders-Practical Interpretation for the Internist

Biological parameter	Typical abnormality	Diagnostic value	Clinical interpretation for the internist
Plasma total homocysteine (tHcy)	↑↑↑ often >100 µmol/L (normal <15)	Pivotal — maximal sensitivity	Most sensitive marker in remethylation or proximal intracellular defects. May be isolated (cblE, cblG, MTHFR deficiency) or combined with MMA (cblC, cblD, cblF, cblJ). Moderate elevation also occurs in nutritional deficiency, CKD, hypothyroidism, and with certain medications — clinical context is essential.
Plasma or urinary methylmalonic acid (MMA)	↑↑ often >1000 µmol/L plasma (normal <0.4 µmol/L)	Pivotal — high specificity	Isolated elevation: adenosylcobalamin synthesis defect (cblA, cblB) or mutase deficiency (MMUT). Combined with tHcy elevation: proximal intracellular defect. Note: CKD can moderately elevate MMA (reduced renal clearance) — interpret in context.
Serum cobalamin (total vitamin B12)	Often NORMAL in intracellular processing defects	MISLEADING — never use alone to exclude!	Major pitfall: serum cobalamin reflects circulating haptocorrin-bound cobalamin, not intracellular utilization. A normal (or even elevated) value does not exclude an IDCM. Never discontinue investigation on the basis of a normal serum B12 if the clinical picture is suggestive.
Holotranscobalamin (HoloTC)	↓ in functional deficiency (TCN2 defects, intracellular processing defects)	Early functional marker	Biologically active fraction bound to transcobalamin II. More sensitive than total B12 for detecting functional intracellular deficiency. Useful when clinical suspicion is high despite normal serum B12.

Full blood count — hematological findings	Macrocytic anemia, hypersegmentation, pancytopenia — or entirely NORMAL!	Inconstant, non-discriminating	Present mainly when the methylcobalamin/methionine synthase pathway is affected. May be completely normal in adenosylcobalamin defects or intracellular trafficking disorders. Absence of megaloblastic anemia must not lead to exclusion of the diagnosis.
Acylcarnitines (C3, C3/C2 ratio)	↑ propionylcarnitine (C3), ↑ C3/C2 ratio	Newborn screening marker; useful in unscreened adults	Detected by tandem mass spectrometry. Useful for diagnosis in adults not screened at birth (methylmalonic acidemias). Available in specialist metabolic laboratories.
Urinary organic acid profile	↑↑ urinary MMA, methylcitrate, 3-OH-propionate	Confirmatory — accessible	Gas chromatography–mass spectrometry of urinary organic acids: confirms MMA excretion and distinguishes organic acidemias. Second-line investigation after plasma measurements.
Plasma methionine	↓ in remethylation defects	Complementary orientating marker	Low in cblC, cblE, cblG, and MTHFR deficiency. Useful for guiding betaine supplementation (methionine normalization as treatment target). Should be measured in the initial specialist work-up.
Erythrocyte / plasma folate	Low in functional ‘folate trap’	Orientating, non-specific	Accumulation of 5-methyl-THF (functional trapping) can lead to low erythrocyte folate despite normal intake. Do not substitute this for a comprehensive metabolic evaluation.
Renal function and proteinuria	CKD, proteinuria (glomerular or tubular)	Non-specific — contextual	Progressive CKD in cblA, cblB, severe cblC, and MMUT. Isolated proteinuria with hematuria in Imerslund–Gräsbeck syndrome. Renal TMA: schistocytes + acute kidney injury + thrombocytopenia.
LDH, haptoglobin, schistocytes	Elevated LDH, undetectable haptoglobin, schistocytes on blood film	TMA — diagnostic emergency	Features of thrombotic microangiopathy: always combine ADAMTS13 assay, complement work-up, AND systematic MMA + tHcy measurement in any suspected aHUS to exclude a treatable underlying IDCM.
Multigene sequencing (NGS panel)	Biallelic pathogenic variants identified	Definitive diagnosis	Targeted multigene panel covering MMACHC, MMAA, MMAB, MMADHC, MTR, MTRR, LMBRD1, ABCD4, MMUT, TCN2, CUBN, AMN, MTHFR. Exome sequencing when panel is negative with high clinical suspicion.

MMA = Methylmalonic Acid; tHcy = Total Plasma Homocysteine; CKD = Chronic Kidney Disease; TMA = Thrombotic Microangiopathy; NGS = Next-Generation Sequencing; THF = Tetrahydrofolate; aHUS = Atypical Hemolytic Uremic Syndrome.

Interpretation of the Biochemical Profile: The Diagnostic Key

- **Isolated MMA Elevation (Normal tHcy):** Direct investigation towards adenosylcobalamin synthesis defects (cblA, cblB) or primary methylmalonyl-CoA mutase deficiency (MMUT). CKD may also modestly elevate MMA due to reduced renal clearance — the degree of elevation and clinical context are essential for correct interpretation [18,20].
- **Isolated tHcy Elevation (Normal MMA):** Consider methylcobalamin synthesis or methionine synthase defects (cblE/MTRR, cblG/MTR), MTHFR deficiency, nutritional folate or cobalamin deficiency, or secondary causes (CKD, hypothyroidism, medications). Differential diagnosis from nutritional deficiency is critical and relies on history, dietary habits, clinical context, and response to treatment [17-19].
- **Combined MMA and tHcy Elevation:** Biochemical fingerprint of proximal intracellular processing defects — most

commonly cblC (MMACHC), but also cblD (MMADHC), cblF (LMBRD1), cblJ (ABCD4) — or absorption/transport defects (transcobalamin, intrinsic factor). This profile mandates urgent referral to a specialist metabolic disease centre [6,14].

- **Differential Diagnosis:** A Syndrome-Based Approach for the Internist

The broad phenotypic heterogeneity of IDCMs, combined with the frequency of normal serum cobalamin concentrations in intracellular processing defects, accounts for the median diagnostic delay estimated at several years in adult cohorts [2,3]. The internist is frequently the first specialist to encounter inaugural presentations. The differential diagnosis below is organized by presenting syndrome, highlighting the essential discriminating elements.

Table 4: Differential Diagnosis of Inherited Cobalamin Disorders According to Clinical Presentation

Differential diagnosis	Arguments in favor	Arguments against IDCM	Discriminating investigations
NEUROLOGICAL AND PSYCHIATRIC PRESENTATIONS			
Multiple sclerosis (MS)	Young adult, relapsing–remitting course, demyelinating white matter lesions on MRI, oligoclonal bands in CSF	No metabolite elevation in MS; renal/hematological involvement absent	Plasma MMA + tHcy (normal in MS); spinal cord MRI (posterior column pattern in IDCM vs periventricular/cervical in MS); CSF analysis; evoked potentials
Nutritional vitamin B12 deficiency (pernicious anemia, malabsorption)	↓ serum B12, ↑ MMA + tHcy, positive anti-intrinsic factor antibodies, anti-parietal cell antibodies	No family history; onset typically >40 years; rapid and complete response to treatment	Anti-intrinsic factor antibodies; gastroscopy; genetic panel if doubt; therapeutic response is discriminating (complete in nutritional deficiency, partial in IDCM)
MTHFR deficiency (severe thermolabile variant)	Isolated ↑ tHcy, ↓ methionine, normal or elevated folates, no MMA elevation	Biochemical profile distinct from cblE/cblG where MMA is also normal; MTHFR deficiency usually lacks MMA elevation	MTHFR genotyping (c.677C>T, c.1298A>C variants), plasma methionine, multigene panel for severe forms
Metachromatic leucodystrophy, adrenoleukodystrophy	Progressive demyelination, long-tract involvement, variable age of onset	Specific biomarkers differ (very long-chain fatty acids, arylsulphatase A)	Very long-chain fatty acids (VLCFA), lysosomal enzyme assays, brain MRI pattern, exome sequencing
Primary psychiatric disorders (schizophrenia, bipolar disorder, refractory depression)	DSM-5 criteria met, family psychiatric history, adolescent onset	No MMA or tHcy elevation; no associated systemic abnormalities	Systematic tHcy + MMA measurement in all young adults with first-episode psychosis or refractory depression before age 40
HEMATOLOGICAL PRESENTATIONS			
Dietary folate deficiency	↑ tHcy, low plasma folates, elevated MCV, nutritional context (alcoholism, malnutrition, pregnancy)	No MMA elevation; no multisystem involvement	Erythrocyte folate + MMA + tHcy + full work-up; rapid and complete response to folate supplementation distinguishes isolated nutritional deficiency
Bone marrow aplasia, myelodysplastic syndrome (MDS)	Pancytopenia, dysplastic or aplastic marrow on biopsy, abnormal cytogenetics	Normal MMA and tHcy in MDS	Bone marrow biopsy + cytogenetics + FISH; normal MMA + tHcy in MDS
VASCULAR AND THROMBOEMBOLIC PRESENTATIONS			
Constitutional thrombophilia (factor V Leiden, protein C/S deficiency)	Family history of thrombosis, identified thrombophilic mutations	No MMA or tHcy elevation; no multivisceral systemic involvement	Full thrombophilia screen + MMA + tHcy; note: IDCM and thrombophilia may coexist — do not stop at the first positive result
Thrombotic microangiopathy (aHUS, TTP)	Schistocytes, thrombocytopenia, acute kidney injury, elevated LDH, undetectable ADAMTS13 (TTP)	Elevated MMA + tHcy points to cblC as underlying cause of TMA	ADAMTS13 activity; complement work-up (C3, C4, factor H, anti-factor H); AND SYSTEMATICALLY MMA + tHcy in any aHUS in a young patient
RENAL PRESENTATIONS			
Glomerulonephritis (membranous, MPGN)	Nephrotic syndrome, glomerular hematuria, specific renal biopsy	Absent IDCM biochemical profile in primary GN	Renal biopsy ± IF + EM + MMA + tHcy to exclude IDCM before initiating immunosuppressive therapy
Tubular nephropathy (Fanconi syndrome, Bartter syndrome)	Tubular acidosis, hypophosphatemia, proximal tubulopathy, salt wasting	Normal MMA and tHcy in primary tubulopathies; Imerslund–Gräsbeck syndrome does present tubular proteinuria	Blood gas + urinary electrolytes + MMA + tHcy + qualitative proteinuria (tubular vs glomerular) + genetics (CUBN/AMN if proteinuria + low serum B12)

MMA = Methylmalonic Acid; tHcy = Total Plasma Homocysteine; IF = Intrinsic Factor; GN = Glomerulonephritis; MPGN = Membranoproliferative Glomerulonephritis; CKD = Chronic Kidney Disease; CSF = Cerebrospinal Fluid; TMA = Thrombotic Microangiopathy; MTHFR = Methylene tetrahydrofolate Reductase; TTP = Thrombotic Thrombocytopenic Purpura; aHUS = Atypical Haemolytic Uraemic Syndrome; MCV = MEAN Corpuscular Volume; MS = Multiple Sclerosis; VLCFA = Very Long-Chain Fatty Acids.

Key Diagnostic Pitfalls -Essential Knowledge for the Internist

- **‘Normal’ Serum Cobalamin-the Primary Pitfall:** In intracellular processing defects (cblC, cblD, cblE, cblG...), circulating cobalamin is normal because the defect lies downstream of absorption. Never use serum B12 alone to exclude an IDCM.
- **Partial or Absent Response to Standard Vitamin B12 Supplementation:** Megaloblastic anemia that fails to respond to oral cyanocobalamin should raise suspicion for an IDCM. Oral cyanocobalamin is ineffective in intracellular defects requiring high-dose parenteral hydroxocobalamin.
- **TMA in a Young Adult:** Any presentation of aHUS in a young patient must include measurement of plasma MMA and tHcy before initiating eculizumab, so as not to miss a treatable cblC-related TMA.
- **First-Episode Psychosis in a Young Adult:** Measure plasma homocysteine systematically in any first psychotic episode or refractory depression in adults under 40 years. Treating an underlying IDCM may achieve complete remission of psychiatric symptoms.
- **‘Unexplained’ Proteinuria Associated with Anemia:** This combination is suggestive of Imerslund–Gräsbeck syndrome (CUBN/AMN variants). Tubular proteinuria associated with low serum cobalamin is virtually diagnostic.
- **Do Not Stop at the First Positive Diagnosis:** Factor V Leiden or moderately elevated homocysteine of nutritional origin may coexist with an IDCM. If clinical response is insufficient or the presentation is atypical, deepen the metabolic work-up.
- **Diagnostic Strategy for the Adult Clinician**

The diagnostic approach in adults begins with a high index of clinical suspicion, followed by a stepwise biochemical and molecular evaluation [17,19,24].

Step 1-First-Line Biochemical Screening

Plasma total homocysteine (tHcy) and plasma or urinary methylmalonic acid (MMA) are the pivotal initial investigations [17-19]. Isolated MMA elevation without hyperhomocysteinaemia indicates impairment of adenosylcobalamin synthesis (cblA, cblB) or methylmalonyl-CoA mutase deficiency (mut⁰/mut⁻). Isolated tHcy elevation without MMA elevation suggests a defect in methylcobalamin synthesis or methionine synthase function (cblE, cblG) or MTHFR deficiency. Combined elevation of both MMA and tHcy is the biochemical fingerprint of proximal intracellular processing defects — most commonly cblC (MMACHC), cblD, cblF, or cblJ — or of absorption and transport disorders.

Critical Practical Point

Serum total cobalamin concentrations are frequently normal or only minimally reduced in inherited intracellular processing defects, because circulating cobalamin concentrations do not reflect intracellular cobalamin utilization. Holotranscobalamin (the biologically active fraction bound to transcobalamin II) may provide a more sensitive functional marker in selected cases and should be measured when clinical suspicion remains high despite apparently normal serum cobalamin [10-27].

Step 2-Confirmatory Molecular Diagnosis

Definitive diagnosis requires molecular genetic testing. Multigene panels or exome-based sequencing covering MMACHC, MMAA, MMAB, MMADHC, MTRR, MTR, LMBRD1, ABCD4, MMUT, TCN2, CUBN, AMN, and MTHFR are preferred, given the substantial phenotypic overlap across complementation groups [17,19]. Functional cell-based complementation assays in

fibroblasts, although less widely available, remain the reference standard for categorization into complementation groups when genotype–phenotype correlation is unclear.

Newborn Screening and Its Implications for the Adult Internist

Tandem mass spectrometry–based newborn screening — detecting elevated propionylcarnitine (C3) and an increased C3/C2 acylcarnitine ratio — identifies most infants with methylmalonic acidemia, including cblC disease, before symptom onset [29,30,31]. Adult internists are increasingly encountering patients diagnosed through such programs who are transitioning from pediatric metabolic services. These patients require long-term multidisciplinary surveillance and may develop new complications (renal, ophthalmological, neurological) in adulthood despite early treatment, underscoring the importance of continued specialist follow-up.

Treatment

Parenteral Hydroxocobalamin: Drug of Choice

For all cobalamin-responsive inherited intracellular processing disorders, parenteral hydroxocobalamin is the treatment of choice over cyanocobalamin, owing to superior plasma retention, cellular uptake, and intracellular conversion efficiency to the active cofactor forms [17,19,32]. In cblC, cblF, and cblJ disease, treatment typically consists of intramuscular or subcutaneous hydroxocobalamin 1 mg daily during acute decompensation, followed by individualized maintenance dosing (several times weekly to daily), guided by plasma tHcy and MMA response.

The choice of cobalamin formulation is crucial in inherited disorders of cobalamin metabolism. Current evidence supports parenteral hydroxocobalamin (OHCbl) as the treatment of choice for nearly all intracellular cobalamin-processing defects. Compared with cyanocobalamin, hydroxocobalamin achieves higher and more sustained tissue concentrations, is more efficiently converted into the active coenzyme forms (methylcobalamin and adenosylcobalamin), and can partially overcome residual intracellular trafficking defects.

Hydroxocobalamin is highly effective in remethylation disorders (particularly cblC disease) and in cobalamin-responsive forms of methylmalonic acidemia, leading to reductions in plasma total homocysteine and methylmalonic acid and improving clinical outcomes. Increasing evidence suggests a dose–response relationship, with higher doses providing superior biochemical control in some patients.

In contrast, cyanocobalamin is not recommended because its activation depends on intracellular pathways that are themselves impaired in these disorders. Likewise, methylcobalamin and adenosylcobalamin have not demonstrated superiority over hydroxocobalamin and currently remain adjunctive or experimental therapies.

For internists, the practical message is straightforward: hydroxocobalamin administered intramuscularly or subcutaneously should be initiated promptly whenever an inherited cobalamin disorder is diagnosed or strongly suspected, and should remain the cornerstone of long-term treatment.

Key point: Hydroxocobalamin is the Preferred and evidence-based form of vitamin B12 for inherited disorders of cobalamin metabolism; cyanocobalamin should generally be avoided, and alternative coenzyme forms have no proven advantage in routine clinical practice.

Adjunctive Therapies

Betaine (trimethylglycine, 2–6 g/day orally) promotes alternative remethylation of homocysteine via the betaine–homocysteine methyltransferase pathway, complementing the methionine synthase-dependent route, and is a standard adjunct in remethylation disorders [6,17]. Folinic acid (vitamin B9) provides additional one-carbon units for the remethylation cycle. Carnitine supplementation is indicated in cases of secondary carnitine depletion associated with organic acidemia. Protein restriction is not routinely indicated in cblC, cblF, or cblJ disorders but may be considered in isolated methylmalonic acidemia with persistent metabolic instability.

Management of Cobalamin-Unresponsive Forms

Isolated methylmalonic acidemia due to methylmalonyl-CoA mutase deficiency (*mut⁰/mut⁻*) is generally cobalamin-unresponsive and is managed conservatively with protein restriction, aggressive prevention of catabolic stress, and carnitine supplementation [20,33]. In contrast, cblA disease retains cobalamin responsiveness and is associated with a more favorable metabolic and clinical outcome under hydroxocobalamin therapy [18,20].

Organ Transplantation

In severe methylmalonic acidemia refractory to optimal medical management, liver transplantation substantially reduces systemic methylmalonic acid burden and the frequency of metabolic crises [22, 25,34]. However, transplantation does not fully normalize metabolite production, and renal and neurological complications may persist post-transplantation, reflecting ongoing extra-hepatic MMA generation. Kidney transplantation provides partial metabolic correction through restoration of enzymatic activity in renal tissue and has been used in selected patients with advanced renal disease [24]. Combined liver–kidney transplantation offers the greatest metabolite reduction in patients with both hepatic and renal dysfunction [22–24].

Emerging Therapies

Adeno-associated viral vector–mediated gene addition, lipid nanoparticle-delivered mRNA encoding methylmalonyl-CoA mutase, and CRISPR-based genome editing strategies are under active preclinical and early clinical investigation [24–34]. Preclinical studies in animal models demonstrate a selective growth advantage for corrected hepatocytes, supporting the feasibility of durable metabolic correction without solid-organ transplantation. These approaches represent the most promising future disease-modifying strategies for cobalamin-unresponsive methylmalonic acidemia [24–34].

Panel: Diagnostic and Therapeutic Approach in Adult Medicine when to Suspect an IDCM in Adults

- Unexplained neurological syndrome (myelopathy, neuropathy, cognitive decline), regardless of age at onset
- Treatment-refractory psychiatric presentation (depression, psychosis) in a young adult <40 years
- Recurrent thromboembolic events without conventional risk factors
- Unexplained renal impairment, proteinuria, or thrombotic microangiopathy (aHUS)
- Normal or mildly abnormal serum cobalamin with hematological or neurological findings
- Megaloblastic anemia without complete response to conventional vitamin B12 or folate supplementation

Stepwise Diagnostic Evaluation

- Step 1 — Plasma tHcy + plasma or urinary MMA: identify the biochemical pattern (isolated or combined)
- Step 2 — Holotranscobalamin if serum B12 is within normal limits but clinical suspicion remains high
- Step 3 — Urinary organic acid profile + plasma acylcarnitines in a specialist metabolic laboratory
- Step 4 — Multigene panel or exome sequencing (MMACHC, MMAA, MMAB, MMADHC, MTR, MTRR, LMBRD1, ABCD4, MMUT, TCN2, CUBN, AMN, MTHFR)
- Step 5 — Refer to a specialist inherited metabolic disease center for treatment initiation and multidisciplinary follow-up

Therapeutic Principles

- Parenteral hydroxocobalamin (1 mg IM or SC daily during decompensation; maintenance individualized)
- Betaine (2–6 g/day orally) as remethylation support in combined disorders
- Folinic acid (vitamin B9) and carnitine as indicated by metabolic profile
- Monitor tHcy and MMA to guide dose adjustment; annual ophthalmological surveillance in cblC disease
For refractory forms: discuss liver or combined liver–kidney transplantation in a multidisciplinary setting

Transition from Pediatric to Adult Care

The transition from pediatric to adult care in inherited metabolic disorders — here, those affecting cobalamin metabolism — represents a critical and increasingly prominent challenge in contemporary metabolic medicine. Advances in diagnostic and therapeutic strategies have transformed many IDCMs from rapidly fatal childhood diseases into chronic, lifelong conditions, resulting in a growing population of adolescents surviving into adulthood who require ongoing specialist care within adult-oriented health systems.

Transition remains heterogeneous and frequently poorly structured, with risks of loss to follow-up, treatment non-adherence, and metabolic instability during late adolescence. Consensus recommendations emphasize that transition should be understood not as a single administrative transfer but as a purposeful, planned, and multidisciplinary process that progressively fosters patient autonomy while ensuring continuity of highly specialized metabolic care across pediatric and adult services [29,30].

Key elements include early initiation of transition planning, joint pediatric–adult clinics, structured education regarding disease self-management, and involvement of internal medicine or adult metabolic specialists experienced in rare diseases. Successful transition requires integration of medical, psychological, and social dimensions, acknowledging the evolving cognitive and emotional maturity of adolescents with IDCMs and the complexity of lifelong dietary, pharmacological, and biochemical monitoring. Despite the availability of expert consensus frameworks, implementation remains inconsistent across health systems, underscoring the need for standardized transition models embedded within national reference networks for rare metabolic diseases.

Conclusions

Inherited disorders of cobalamin metabolism, long regarded as exclusively pediatric entities, represent a genuinely relevant diagnostic consideration for adult physicians and internists. The protean clinical manifestations—neuropsychiatric, thromboembolic, renal, and hematological - combined with the frequently normal

serum cobalamin concentrations in intracellular processing defects, create a diagnostic gap that results in years of delay and preventable irreversible organ damage.

The diagnostic key is biochemical: plasma total homocysteine and methylmalonic acid, two readily available tests, provide the metabolic fingerprint that localizes the defect before confirmatory molecular analysis. Treatment with parenteral hydroxocobalamin, initiated promptly in confirmed or highly suspected cases, can halt and partially reverse multisystem complications. Even in delayed or advanced disease, treatment reduces metabolic burden and stabilizes progression.

As expanded newborn screening programs generate a growing cohort of adult survivors with IDCMs, and as gene-based and mRNA therapies advance towards clinical use, internists and adult metabolic medicine specialists must develop familiarity with these conditions. Collaborative management involving internal medicine, neurology, nephrology, ophthalmology, and inherited metabolic disease services remains essential to optimize long-term outcomes in this challenging but increasingly manageable group of disorders [23,26,30,32,35,29,41].

Contributors

EA conceived and supervised the work, provided critical intellectual revision, and approved the final manuscript. JET and NLV contributed to literature review, data synthesis, and drafting. All authors critically revised the manuscript and approved the final version. Data sources and tools: Literature review and manuscript preparation were informed by structured searches of PubMed and Google Scholar. Reference management was performed using EndNote. Artificial intelligence-assisted drafting and language refinement were performed using ChatGPT and Claude (Anthropic) as supportive tools; all scientific content was verified and curated by the authors.

Declaration of interests

The authors declare no competing interests.

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