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Advances in the Treatment of Vitamin B12 Deficiency—from Classical Replacement to Precision Supplementation

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Introduction

Vitamin B12 deficiency remains a common and clinically significant condition, affecting hematologic, neurologic, and systemic health. Despite being preventable and easily treatable, its management continues to evolve as understanding of metabolism, absorption, and individualized therapy improves [1]. The principal therapeutic goal is to restore adequate vitamin B12 levels to reverse anemia, prevent neurological complications, and maintain metabolic balance. Modern strategies now integrate precision supplementation, focusing on bioavailability, patient compliance, and mechanistic understanding.

Hematological Aspects of Vitamin B12 Deficiency

Vitamin B12 plays an essential role in DNA synthesis and red blood cell maturation. Its deficiency leads to defective thymidylate synthesis, resulting in nuclear-cytoplasmic asynchrony within erythroid precursors and causing megaloblastic anemia [1]. Peripheral blood smears typically reveal macrocytosis, anisopoikilocytosis, and hypersegmented neutrophils, while bone marrow aspirates show megaloblastic hyperplasia.

Recent hematological studies using digital imaging and machine learning techniques have enhanced early detection of macrocytosis and subclinical marrow dysplasia, allowing diagnosis before overt anemia occurs [1]. In elderly or chronically ill patients, vitamin B12 deficiency often coexists with inflammation or folate deficiency, producing mixed anemia syndromes. Therapeutic response is both rapid and diagnostic: reticulocytosis typically emerges within 5–7 days, followed by normalization of hemoglobin and MCV within several weeks [1]. Persistent cytopenias after replacement therapy should raise suspicion of myelodysplasia or secondary marrow disorders. Moreover, neurological damage may remain irreversible if treatment is delayed, underscoring the importance of early detection and intervention.

Advanced diagnostic algorithms combining hematologic parameters, metabolic biomarkers (methylmalonic acid, homocysteine, holotranscobalamin), and AI-assisted analysis improve diagnostic accuracy and help distinguish functional from true deficiency [1].

Forms of Vitamin B12 Supplementation

Therapeutic formulations of vitamin B12 include cyanocobalamin, hydroxocobalamin, and methylcobalamin, each with distinct pharmacokinetic and pharmacodynamic properties (**Table 1**) [2–4]. Cyanocobalamin, the synthetic form, remains widely used due to its stability and affordability, though it requires metabolic conversion into active coenzymes, which may be suboptimal in patients with absorption or enzymatic defects [1,4]. Hydroxocobalamin, a natural form with higher bioavailability and longer systemic retention, is preferred in pernicious anemia, malabsorption syndromes, and severe deficiency. It also allows less frequent dosing due to its prolonged plasma half-life [1]. Methylcobalamin, the active coenzyme form, directly participates in neuronal methylation processes and is particularly indicated in neurological complications such as peripheral neuropathy or cognitive decline [2,3]. Comparative trials indicate that methylcobalamin enhances neuroregeneration and improves functional recovery.

Table 1. Comparative overview of vitamin B12 forms, routes of administration, pharmacokinetics, and clinical applications.

Form / Route	Type / Form	Typical Dosage	Bioavailability / Kinetics	Indications / Use Case	Advantages	Limitations
Cyanocobalamin IM	Synthetic	1000 µg/day × 1–2 weeks → weekly/monthly	Requires enzymatic conversion to methylcobalamin / adenosylcobalamin	Severe deficiency, malabsorption, pernicious anemia	Widely available, cost-effective, stable	Less effective if malabsorption or enzymatic defect
Cyanocobalamin Oral	Synthetic	1000–2000 µg/day	Partial absorption (~1–2% at high doses)	Mild/moderate deficiency, long-term maintenance	Convenient, non-invasive, cost-effective	Low absorption in GI disorders
Hydroxocobalamin IM / IV	Natural, biologically active	1000 µg/day × 1–2 weeks → less frequent maintenance	High bioavailability, longer plasma retention	Severe deficiency, poor GI absorption, pernicious anemia, post-GI surgery	Fewer injections, better retention, binds cyanide (therapeutic for poisoning)	More expensive, limited availability
Methylcobalamin IM / Oral	Active coenzyme	1000–2000 µg/day	Directly bioactive; no conversion required	Neurological complications (peripheral neuropathy, cognitive dysfunction)	Direct neuronal effect, promotes nerve regeneration	Oral less available, higher cost
Sublingual	Synthetic or methylcobalamin	1000–2000 µg/day	Absorbed via oral mucosa, bypassing GI tract	Malabsorption, injection intolerance	Non-invasive, avoids GI degradation	Limited availability in some regions
Intranasal	Synthetic or methylcobalamin	500–1000 µg/application, 1–2× weekly	Rapid mucosal absorption	Pernicious anemia, neurological involvement	Non-invasive, convenient	Requires adherence, limited regional availability
Transdermal patch	Synthetic	1000–2000 µg/day	Controlled, steady release	Chronic deficiencies, patient preference	Non-invasive, sustained release	Efficacy and long-term data limited
Intradermal	Synthetic / experimental	As per protocol	Rapid absorption, less invasive than IM	Under investigation for routine therapy	Reduced discomfort, faster absorption	Research phase, not widely available
Gastrostomy tube	Synthetic	Individualized	Direct delivery, reliable absorption	Dysphagia, neurological impairment, feeding tube patients	Effective for patients unable to swallow	Requires tube placement, clinical supervision

IM: Intramuscular; IV: Intravenous

Routes of Administration

The choice of administration route is crucial for therapeutic efficacy, rate of correction, and adherence. Intramuscular (IM) and intravenous (IV) administration remain gold standards, especially for severe deficiency or impaired absorption [1,5]. Standard IM therapy—1000 µg daily for 1–2 weeks—ensures reliable absorption by bypassing gastrointestinal barriers, while IV delivery is reserved for acute or life-threatening presentations. For mild or moderate deficiency with intact absorption, oral supplementation (1000–2000 µg/day) provides effective and convenient treatment [1]. A 2023 network meta-analysis found that IM and sublingual routes achieved the fastest increases in serum vitamin B12, though oral therapy remained effective for long-term management [5]. Sublingual and intranasal formulations offer non-invasive alternatives for patients with malabsorption, gastrointestinal surgery, or injection intolerance [2]. Novel transdermal and intradermal systems are under investigation for sustained release and improved adherence [5]. In addition, Sucrosomial® B12, a new oral delivery system, has shown bioavailability comparable to parenteral therapy, expanding non-invasive options [1].

Dosage and Duration

Treatment protocols vary with deficiency severity, route, and patient profile [1,5].

Mild to moderate deficiency: oral supplementation of 250–1000 µg/day for at least 4 months is recommended.

Severe or neurologically symptomatic deficiency: 1000–2000 µg/day IM or IV for 1–2 weeks, followed by weekly to monthly maintenance.

Long-term management: monthly IM or IV injections, or daily oral supplementation when absorption is adequate.

Special populations such as elderly individuals, pregnant women, vegetarians, and post-gastrointestinal surgery patients may require lifelong supplementation.

Allergy and Hypersensitivity

Allergic reactions to vitamin B12 are rare but clinically relevant, particularly with cyanocobalamin. In such cases, switching to hydroxocobalamin or methylcobalamin is advised [1,3]. When injection-related hypersensitivity occurs, oral, sublingual, or intranasal administration may be safer alternatives. Antihistamine pre-treatment may also be considered for mild reactions under medical supervision [1].

Future Perspectives

Emerging directions in vitamin B12 therapy focus on personalized medicine, accounting for genetic polymorphisms (MTRR, MTHFR), microbiome composition, and comorbidities affecting absorption and metabolism [1,6]. Future strategies will likely integrate multimodal monitoring—including hematologic, metabolic, and neurologic outcomes—to define individualized, precision supplementation protocols.

Artificial intelligence will play a growing role in screening and interpretation of diagnostic data, enhancing early recognition and treatment monitoring. The ultimate goal is to move from correction of deficiency to optimization of vitamin B12 metabolism as part of comprehensive metabolic health management.

Conflict of Interest

None.

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