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Vitamin B12 Deficiency: Current Therapeutic Approaches and Emerging Strategies

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Abstract

Vitamin B12 (cobalamin) is an essential micronutrient involved in DNA synthesis, erythropoiesis, and neurological function. Deficiency can result in hematological, neurological, and psychiatric manifestations, potentially leading to severe and irreversible complications if untreated. This editorial reviews current therapeutic strategies for vitamin B12 deficiency, including conventional supplementation forms, recommended dosages, and treatment durations. Additionally, emerging administration routes—sublingual, intranasal, transdermal, intradermal, and gastrostomy—are explored for their potential to enhance patient compliance and therapeutic efficacy. Special considerations in high-risk populations, including the elderly, pregnant women, and patients with gastrointestinal disorders, are also discussed. Optimizing therapeutic strategies for B12 deficiency is critical for improving patient outcomes and quality of life.

Keywords: Vitamin B12, Cobalamin, Cyanocobalamin, Anemia

Introduction

Vitamin B12 deficiency, cobalamin deficiency, affects an estimated 5–20% of the population and can manifest with a spectrum of hematological, neurological, and psychiatric manifestations. As a critical cofactor in DNA synthesis and nervous system function, B12 is indispensable for red blood cell production and neuronal integrity. Deficiency can lead to megaloblastic anemia, neuropathy, cognitive impairment, and psychiatric disturbances, significantly affecting quality of life [1]. Certain populations are at higher risk, including older adults with reduced absorption capacity, vegetarians and vegans, and individuals with food-cobalamin malabsorption or pernicious anemia (Biermer's disease) [2]. Timely identification and appropriate management are essential to prevent irreversible neurological damage. Traditional supplementation methods, primarily intramuscular cyanocobalamin injections, have been the cornerstone of therapy. However, evolving strategies, including oral, sublingual, intranasal, transdermal, and intradermal routes, offer novel avenues to enhance patient adherence and clinical outcomes [3].

Hematological Manifestations

Vitamin B12 deficiency profoundly affects hematopoiesis due to its essential role in DNA synthesis and cell division [1]. The hallmark hematological manifestation is megaloblastic anemia, characterized by macrocytic red blood cells, increased mean corpuscular volume (MCV > 100 fL), and hypersegmented neutrophils. Ineffective erythropoiesis leads to intramedullary hemolysis, resulting in elevated lactate dehydrogenase (LDH) and indirect bilirubin levels, decreased haptoglobin levels. Clinically, patients often present with fatigue, pallor, dyspnea on exertion, and tachycardia, reflecting reduced oxygen-carrying capacity [4]. Severe or prolonged deficiency can progress to pancytopenia, involving leukopenia and thrombocytopenia, which increase susceptibility to infections and bleeding tendencies. Pseudo-thrombotic micro-angiopathy is also reported in relation to cobalamin deficiency. Bone marrow examinations typically reveal megaloblastic changes with nuclear-cytoplasmic asynchrony in erythroid precursors. Additional laboratory features may include elevated homocysteine and methylmalonic acid levels, which serve as

sensitive markers for B12 deficiency [4]. Prompt recognition and treatment are critical, as sustained deficiency can cause irreversible bone marrow suppression and hematological complications, whereas timely supplementation usually results in rapid hematologic recovery within weeks [4].

Therapeutic Forms of Vitamin B12

The three primary therapeutic forms of vitamin B12—cyanocobalamin, hydroxocobalamin, and methylcobalamin—each possess distinct pharmacokinetic and clinical profiles (**Table 1**) [1,3]. Cyanocobalamin, the most commonly used synthetic form, is favored for its stability, cost-effectiveness, and widespread availability, and can be administered intramuscularly, orally, or nasally; it is converted *in vivo* to active forms, methylcobalamin and adenosylcobalamin, although absorption may be suboptimal in patients with gastrointestinal disorders. Hydroxocobalamin, a naturally occurring form, is preferred in severe deficiencies or in individuals with poor oral absorption, providing higher bioavailability and prolonged retention, which allows for fewer injections; it is particularly useful in conditions such as pernicious anemia and Crohn's disease. Methylcobalamin, the biologically active coenzyme form, bypasses conversion requirements and directly supports neurological repair and function, making it the preferred choice for managing neurological complications such as neuropathy and cognitive deficits, and it can be administered via injection or orally [3].

Routes of Administration

The choice of vitamin B12 administration route depends on deficiency severity, gastrointestinal absorption, patient preference, and adherence considerations (**Table 2**) [1,3]. Intramuscular (IM) injections remain the gold standard for severe deficiency or malabsorption, with initial daily doses

Table 1. Forms of vitamin B12 supplementation.

Form	Type	Common Uses	Route	Advantages	Limitations
Cyanocobalamin	Synthetic	Standard treatment for general deficiency	IM, oral, nasal	Stable, cost-effective, widely available	Requires conversion to active forms; less effective in malabsorption
Hydroxocobalamin	Natural, biologically active	Severe deficiency, poor absorption, pernicious anemia	IM, IV	Higher bioavailability, longer retention, fewer injections	More expensive; less available than cyanocobalamin
Methylcobalamin	Active coenzyme	Neurological complications	IM, oral	Direct neurological effects, supports nerve regeneration	More costly; oral form less available than cyanocobalamin

Table 2. Routes of vitamin B12 administration.

Route	Typical Dose	Advantages	Limitations	Clinical Indications
IM	1,000 µg/day (1–2 weeks), then 1,000 µg/week (4 weeks), then 1,000 µg/monthly	Rapid absorption; bypasses gut	Requires injections; less convenient	Severe deficiency, pernicious anemia, malabsorption
IV	1,000 µg/day or several times/week	Immediate correction; high plasma levels	Clinical setting required	Acute/severe deficiency with neurological symptoms
Oral	1,000–2,000 µg/day	Convenient; cost-effective	Less effective in malabsorption	Mild/moderate deficiency, long-term maintenance
Sublingual	1,000–2,000 µg/day	Bypasses gut; easy to use	Limited availability	Malabsorption, swallowing difficulties
Intranasal	500–1,000 µg/application, 1–2x/week	Non-invasive; effective	Limited availability; adherence needed	Pernicious anemia, neurological involvement
Transdermal	1,000–2,000 µg/day (patch)	Sustained release; non-invasive	Efficacy requires further research	Chronic deficiencies, patient preference
Intradermal	Research phase	Less invasive than IM; rapid absorption	Limited availability; still investigational	Under study for frequent dosing
Gastrostomy	Individualized	Ensures delivery when oral not feasible	Requires tube placement	Dysphagia, neurological impairment, feeding tube patients

of 1,000 µg for 1–2 weeks, then 1,000 µg/weekly for 4 weeks, followed by monthly maintenance, providing rapid and reliable restoration of B12 levels, particularly in patients with pernicious anemia. Intravenous (IV) administration is reserved for acute or severe deficiencies, especially when neurological involvement is present, allowing immediate systemic availability [1]. Oral supplementation, typically 1,000–2,000 µg daily, is effective and convenient for patients with intact gastrointestinal function and mild to moderate deficiency [1,3]. Sublingual administration bypasses the digestive tract, offering an effective alternative for malabsorption, with comparable efficacy to oral tablets and improved adherence. Intranasal delivery provides 500–1,000 µg per application once or twice weekly, serving as a non-invasive option for patients with absorption challenges or needle aversion [3]. Transdermal patches, an emerging modality, offer steady, sustained B12 delivery and are particularly promising for long-term supplementation in patients preferring non-invasive therapy. Intradermal injections, still under investigation, appear to offer comparable efficacy to IM injections with improved patient comfort. For patients unable to swallow, gastrostomy tube administration ensures reliable B12 delivery, addressing needs in cases of dysphagia or severe neurological impairment [3].

Dosage, Duration, and Special Populations

Treatment regimens vary according to severity (**Table 3**) [1]. Mild to moderate deficiency typically responds to oral supplementation (250–1,000 µg/day for ≥4 months), whereas severe deficiency requires high-dose IM or IV therapy (1,000 µg/day initially, potentially up to 2,000 µg for neurological symptoms). Long-term maintenance may involve monthly IM or IV injections or daily oral supplementation, depending on absorption capacity and patient preference [1,3].

Special populations require tailored approaches. The elderly may require higher or more frequent dosing due to impaired absorption. Pregnant women need adequate supplementation to support fetal neurodevelopment. Individuals with gastrointestinal disorders, including post-bariatric surgery patients, often require parenteral administration. Vegetarians and vegans typically respond well to oral supplementation but require dietary counseling and monitoring [4].

Allergies and Non-response Management

Allergic reactions to B12 formulations are rare. In cases of hypersensitivity to cyanocobalamin, hydroxocobalamin or methylcobalamin may be used, with alternative routes such as oral, sublingual, or intranasal forms considered to mitigate reaction risk. Pre-treatment with antihistamines or corticosteroids may be appropriate in mild cases under clinical supervision. Non-response or non-compliance should prompt reevaluation of administration routes, dosing schedules, and patient education. Switching to parenteral or alternative non-invasive routes may improve adherence and therapeutic outcomes [3].

Special Considerations

Certain populations require tailored approaches to vitamin B12 supplementation. Elderly patients may need higher or more frequent dosing due to impaired absorption, while pregnant women require adequate supplementation to prevent maternal and fetal complications. Vegetarians and vegans generally respond well to oral supplementation, though education on diet and fortified foods is important to maintain sufficient B12 levels. Patients with gastrointestinal disorders, including those who have undergone bariatric surgery or have malabsorption syndromes, often require parenteral therapy to ensure effective correction of deficiency [4].

Expert Opinion

Vitamin B12 deficiency remains an underdiagnosed condition with significant clinical consequences, particularly in vulnerable populations such as the elderly, pregnant women, and patients with malabsorption syndromes. From a clinical perspective, early recognition of hematological and neurological manifestations is essential to prevent irreversible

Table 3. Dosage and duration of vitamin B12 therapy.

Scenario	Dose	Duration	Route	Notes
Mild/moderate deficiency	250–1,000 µg/day	≥4 months	Oral/sublingual	Monitor B12 levels; effective if absorption intact
Severe deficiency	1,000 µg/day (initial)	1–2 weeks	IM/IV	Up to 2,000 µg/day if neurological symptoms present
Long-term maintenance	1,000–2,000 µg/day or monthly IM/IV	Lifetime in some cases	Oral/IM/IV	Tailor to absorption and patient preference
Special populations	Adjusted individually	Variable	Oral/IM/IV	Elderly, pregnant women, GI disorders, vegetarians

complications [1,3]. While IM cyanocobalamin remains the gold standard for severe deficiency, emerging routes of administration—including sublingual, intranasal, and transdermal formulations—offer effective, patient-centered alternatives that may improve adherence and quality of life. Oral cobalamin therapy may be discussed in relation to the high frequency of food-cobalamin malabsorption, especially in elderlies (gastric atrophy, *Helicobacter pylori* infection, proton pump inhibitors, and metformin long-term intake) [5]. Methylcobalamin, given its direct role in neurological repair, should be considered in cases with prominent neuropathic or cognitive deficits [3]. Treatment strategies must be individualized, accounting for absorption capacity, severity of deficiency, and patient preference, while long-term monitoring ensures sustained correction. Overall, integrating novel delivery methods with traditional approaches represents a paradigm shift in optimizing therapy for vitamin B12 deficiency, balancing efficacy, safety, and patient convenience.

Conclusion

Effective management of vitamin B12 deficiency requires an individualized approach considering severity, neurological involvement, and absorption capacity. While traditional IM or IV therapy remains essential for severe cases, emerging routes—sublingual, intranasal, and transdermal—offer promising alternatives that enhance adherence and patient convenience. Tailoring therapy to patient-specific factors, including special populations and comorbidities, ensures optimal clinical outcomes. Ongoing research into novel delivery systems will continue to refine management strategies, ultimately improving patient quality of life and global accessibility to effective B12 therapy.

Conflict of Interest

The authors declare no conflicts of interest related to the content of this editorial.

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