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Review Article

Iron Deficiency Anemia of Digestive Origin without Overt Hemorrhage: From Celiac Disease and Helicobacter pylori to Pernicious Anemia, Tea Consumption, Pica, Heyde Syndrome, and Hereditary Hemorrhagic Telangiectasia

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Abstract

Iron deficiency anemia (IDA) is the most prevalent nutritional deficiency worldwide, yet its etiology frequently escapes detection when overt gastrointestinal hemorrhage is absent. A heterogeneous spectrum of digestive conditions — operating through malabsorption, achlorhydria, competitive luminal inhibition, chronic mucosal inflammation, and acquired coagulopathy — accounts for a clinically important and systematically under investigated subset of IDA. This review examines eight major non-hemorrhagic or occult-hemorrhagic digestive causes of IDA: celiac disease, Helicobacter pylori gastritis, autoimmune atrophic gastritis and pernicious anemia (Biermer disease), dietary polyphenol consumption (tea), pica and pagophagia, Heyde syndrome, and hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber disease). For each condition, we detail the pathophysiology of iron depletion, the optimal diagnostic strategy integrating serological, endoscopic, and genetic approaches, and the evidence-based therapeutic management including the pivotal role of intravenous iron formulations when oral supplementation is insufficient or contraindicated. A unified diagnostic algorithm is proposed to guide clinicians in the systematic evaluation of IDA without evident hemorrhage. Recognition of these non-hemorrhagic causes is essential to avoid diagnostic delay, minimize transfusion exposure, and ensure targeted treatment of the underlying condition alongside iron repletion.

KEY CLINICAL POINTS

- *Iron deficiency anemia (IDA) without overt gastrointestinal bleeding represents a clinically underappreciated diagnostic challenge; non-hemorrhagic digestive causes — malabsorption, mucosal inflammation, and competitive inhibition of absorption — are responsible for a substantial proportion of unexplained or refractory IDA.*
- *Celiac disease should be systematically excluded in all patients with unexplained IDA: anti-tissue transglutaminase IgA (anti-tTG IgA) with total IgA measurement is the recommended first-line serological screen, followed by upper endoscopy with duodenal biopsies in seropositive cases.*
- *Helicobacter pylori infection impairs iron absorption through multiple mechanisms — gastric acid suppression, competition for luminal iron, and upregulation of hepcidin — and eradication alone may normalize hemoglobin in H. pylori–associated IDA without iron supplementation.*
- *Pernicious anemia (Biermer disease) and autoimmune atrophic gastritis produce iron deficiency through achlorhydria-mediated impairment of ferric-to-ferrous iron reduction; coexisting vitamin B12 deficiency masks the microcytic pattern, and combined deficiency should be sought in all patients with autoimmune gastritis.*
- *Hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber) and Heyde syndrome cause IDA through a combination of chronic occult mucosal bleeding and, in Heyde syndrome, acquired von Willebrand factor deficiency; aortic valve replacement or TAVI resolves the coagulopathy and reduces GI blood loss.*
- *Dietary and behavioral factors — habitual tea consumption, pica (particularly pagophagia), and strict vegan diets without supplementation — are modifiable causes of IDA that are frequently overlooked in clinical practice.*

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Introduction

The clinical encounter with unexplained iron deficiency anemia (IDA) is among the most common in internal medicine, hematology, and gastroenterology [1]. In the majority of affected adults — particularly men and postmenopausal women — a gastrointestinal source of blood loss is presumed and is actively sought through bidirectional endoscopy. This investigative reflex, while appropriate, carries an inherent diagnostic bias: it presupposes hemorrhage as the mechanism of iron depletion and may defer or omit investigation of non-hemorrhagic etiologies that are equally prevalent and sometimes more treatable.

Non-hemorrhagic digestive causes of IDA operate through three principal mechanisms. The first is malabsorption — the failure of the proximal small-bowel mucosa to absorb dietary iron at a rate sufficient to meet physiological demands, as occurs classically in celiac disease and after surgical bypass of the duodenum [2,22]. The second is achlorhydria — the absence of gastric acid, which is required for solubilization of dietary ferric iron (Fe^{3+}) and its reduction to the absorbable ferrous form (Fe^{2+}), as occurs in autoimmune atrophic gastritis, Helicobacter pylori–induced corpus gastritis, and long-term proton pump inhibitor (PPI) use [4,6,7]. The third mechanism is competitive inhibition or iron sequestration in the intestinal lumen, exemplified by dietary polyphenols (tea tannins) and pica-related geophagia [8–11].

Superimposed on these malabsorptive mechanisms, certain vascular disorders — such as Heyde syndrome and hereditary hemorrhagic telangiectasia — produce chronic occult or intermittent mucosal blood loss that may be entirely inapparent clinically and remain undetected by standard endoscopic evaluation [12–17].

This review adopts a disease-by-disease approach, examining the pathophysiology, diagnosis, and management of each condition, followed by an integrated diagnostic framework. The goal is to equip the clinician with a systematic and evidence-based toolkit for the workup of IDA when overt hemorrhage is absent and standard investigations have proven unrevealing.

Physiology of Dietary Iron Absorption: Key Concepts

A concise review of the physiology of iron absorption is prerequisite to understanding the mechanisms by which each condition in this review produces iron depletion [1]. Dietary iron exists in two forms: heme iron (from hemoglobin and myoglobin in red meat, poultry, and fish), which is absorbed intact via the heme carrier protein 1 (HCP1) with an efficiency of 15 to 35%; and non-heme iron (from plant sources, dairy, eggs, and fortified foods), which requires solubilization in the gastric lumen and reduction from ferric (Fe^{3+}) to ferrous (Fe^{2+}) form by gastric acid and duodenal cytochrome b (DcytB) before uptake via the divalent metal transporter 1 (DMT1) at the apical brush border of duodenal enterocytes [1,6,7].

Bioavailability of non-heme iron ranges from 1 to 10% under normal conditions and is profoundly sensitive to luminal enhancers (ascorbic acid, meat proteins, organic acids) and inhibitors (phytates, oxalates, calcium, polyphenols, and achlorhydria) [8,9].

At the basolateral membrane, absorbed iron is exported into the portal circulation by ferroportin (FPN1/SLC40A1), with hephaestin facilitating re-oxidation to Fe^{3+} for transferrin binding. Systemic iron homeostasis is orchestrated by hepcidin (HAMP), a 25-amino acid hepatic peptide that binds ferroportin and targets it for internalization and degradation, thereby inhibiting iron export from enterocytes, hepatocytes, and macrophages [1].

Hepcidin is upregulated by iron loading, inflammation (via IL-6 and STAT3 signaling), and infection (including H. pylori) [4,7], and is suppressed by iron deficiency, hypoxia, and erythropoietic demand. The hepcidin–ferroportin axis provides a mechanistic explanation for impaired iron absorption and recycling observed in chronic inflammatory states, even when dietary iron intake is adequate — a condition referred to as functional iron deficiency or iron-restricted erythropoiesis [1].

Celiac Disease

Pathophysiology of Iron Deficiency in Celiac Disease

Celiac disease is a systemic immune-mediated enteropathy triggered by dietary gluten in genetically susceptible individuals (HLA-DQ2.5, DQ2.2, or DQ8 haplotypes), affecting approximately 1% of the general population in Western countries [2,22]. The cardinal intestinal lesion — villous atrophy with crypt hyperplasia and intraepithelial lymphocytosis, classified by the modified Marsh-Oberhuber grading system — involves the duodenum and proximal jejunum, precisely the segment responsible for physiological non-heme iron absorption [3].

The severity of IDA correlates directly with the degree of villous atrophy (Table 2): patients with Marsh 3c (total villous atrophy) may present with severe anemia, absent iron stores, and markedly reduced transferrin saturation [2].

Multiple mechanisms converge to produce iron depletion in celiac disease. The primary mechanism is a reduction in absorptive surface area: loss of functional villi dramatically reduces the expression of DMT1 and DcytB, impairing luminal ferric iron reduction and enterocyte uptake [1,22]. Secondary mechanisms include increased intestinal permeability with enterocyte apoptosis, impaired expression of ferroportin at the basolateral membrane, and elevated hepcidin in the context of chronic mucosal inflammation [1,22].

Additionally, patients with celiac disease frequently have concurrent folate (vitamin B9) and vitamin B12 (cobalamin) deficiency, which may mask microcytosis by producing a dimorphic or normocytic blood picture — the so-called "double deficiency" masking pattern that can delay diagnosis [2].

Diagnosis

Celiac disease should be suspected in any patient with unexplained IDA, particularly when associated with symptoms of malabsorption (diarrhea, steatorrhea, bloating, weight loss), short stature, osteoporosis, aphthous stomatitis, dermatitis herpetiformis, or unexplained infertility [2,22]. However, "silent" or "non-classical" celiac disease presenting exclusively as IDA — without prominent gastrointestinal symptoms — accounts for a substantial proportion of cases identified through systematic screening [2].

The recommended first-line serological investigation is anti-tissue transglutaminase IgA (anti-tTG IgA), measured with simultaneous total serum IgA to exclude IgA deficiency (present in ~2% of celiac patients and associated with false-negative serology) [2]. Anti-endomysial IgA and anti-deamidated gliadin peptide (DGP) IgG/IgA provide complementary sensitivity [2].

Confirmatory upper endoscopy with at least four duodenal biopsies (two from the duodenal bulb, two from the second portion) is mandatory in seropositive adults before initiating a gluten-free diet [2,3]. Endoscopic findings suggestive of villous atrophy include scalloping or fissuring of the duodenal folds,

mosaic mucosal pattern, and reduced fold height — features with high positive predictive value when performed in experienced centers [3].

Video capsule endoscopy (VCE) provides a complementary, non-invasive evaluation of the entire small bowel and can reveal similar abnormalities, including mucosal scalloping, mosaic patterns, villous atrophy, and, in more advanced cases, ulcerations or areas of denuded mucosa. Its particular strength lies in detecting the extent and distribution of mucosal involvement beyond the duodenum, especially in patients with suspected or complicated celiac disease. However, while VCE is sensitive for macroscopic changes, it does not replace histological confirmation obtained by duodenal biopsies [2].

Management

The cornerstone of celiac disease management is strict, lifelong adherence to a gluten-free diet (GFD) [2,22]. Iron absorption begins to recover within 4 to 6 weeks of GFD initiation as the duodenal mucosa regenerates, and hemoglobin normalizes in the majority of patients with uncomplicated IDA within 6 to 12 months [2]. However, in patients with severe IDA (hemoglobin <8 g/dL), extensive Marsh 3b/3c atrophy, or inadequate dietary iron intake, intravenous (IV) iron is required because the healing mucosa remains transiently malabsorptive and oral supplementation is often insufficient [1,20,21]. A practical clinical rule is to reassess iron status at 3 months on GFD: patients who fail to demonstrate a ≥2 g/dL hemoglobin rise merit IV iron infusion [1,20].

Refractory celiac disease (RCD) — defined as persistent or recurrent malabsorptive symptoms and villous atrophy despite strict GFD adherence for >12 months, after exclusion of other causes — is classified into type I (normal intraepithelial lymphocyte phenotype) or type II (aberrant clonal intraepithelial lymphocyte population), the latter carrying a significant risk of enteropathy-associated T-cell lymphoma (EATL) [22]. All patients with refractory IDA on a gluten-free diet should undergo reassessment for RCD, evaluation of dietary compliance by a specialized dietitian, and exclusion of other coexisting intestinal disorders [22].

Helicobacter pylori Gastritis

Pathophysiology

H. pylori, a gram-negative spiral bacterium colonizing the gastric mucosa of approximately 44% of the global population, is now firmly established as an independent etiological factor in IDA beyond its role as a cause of gastric hemorrhage [4,6,7]. The pathophysiological mechanisms through which H. pylori produces iron deficiency without overt bleeding are multiple and interactive.

The primary mechanism is impairment of gastric acid secretion. H. pylori corpus gastritis — particularly the atrophic phenotype associated with environmental metaplastic atrophic gastritis (EMAG) — reduces parietal cell mass and diminishes hydrochloric acid production, impairing solubilization of dietary non-heme iron and its reduction from Fe^{3+} to the absorbable Fe^{2+} form [6,7]. A second mechanism involves direct iron sequestration by the bacterium: H. pylori expresses lactoferrin-binding proteins, iron-regulated outer membrane proteins (FrpB/HopA), and siderophore-independent iron acquisition systems that compete with host iron-binding proteins for luminal and gastric mucosal iron [4,7].

Third, H. pylori infection upregulates hepcidin synthesis through IL-6-mediated STAT3 activation, inducing a functional iron deficiency state that reduces intestinal iron absorption and macrophage iron recycling even in the absence of significant anemia [1,7]. Fourth, chronic gastric mucosal inflammation increases iron consumption by inflammatory cells and generates oxidative mucosal injury that impairs iron handling and recycling.

Additionally, H. pylori infection is frequently associated with concurrent vitamin B12 deficiency (food-cobalamin malabsorption), which may mask microcytosis by producing a dimorphic or normocytic blood picture — the so-called "double deficiency" masking pattern that can delay diagnosis [6,7].

Clinical Evidence

Multiple meta-analyses have demonstrated a statistically significant association between H. pylori seropositivity and IDA

Table 1. *Marsh-Oberhuber Histological Classification of Celiac Disease and Correlation with Iron Deficiency Severity.*

Marsh Grade	Histological Features	Association with IDA	Clinical Implication
0 (Normal)	Normal villous architecture; normal IEL count	None	Celiac disease excluded on biopsy
1 (Infiltrative)	Normal villi; IEL >25/100 enterocytes	Mild; early	May represent latent celiac disease; GFD trial warranted
2 (Hyperplastic)	Crypt hyperplasia; normal villi	Moderate	Intermediate; GFD indicated
3a (Partial villous atrophy)	Partial villous atrophy; crypt hyperplasia; ↑IEL	Moderate–severe	Classic celiac; GFD mandatory
3b (Subtotal villous atrophy)	Subtotal villous atrophy	Severe IDA common	GFD + IV iron; monitor for lymphoma
3c (Total villous atrophy)	Complete villous atrophy; flat mucosa	Severe refractory IDA	IV iron; assess for RCD type I/II; consider immunosuppression

IEL denotes intraepithelial lymphocytes; GFD, gluten-free diet; RCD, refractory celiac disease. Marsh grading reflects intestinal mucosal injury severity assessed on duodenal biopsy.

independent of gastric hemorrhage [4,7]. A landmark systematic review and meta-analysis encompassing 16 studies found that H. pylori–positive individuals had significantly lower serum ferritin and hemoglobin values than seronegative controls [4]. Prospective randomized trials have subsequently shown that H. pylori eradication alone — without iron supplementation — normalizes hemoglobin in 30 to 50% of H. pylori–associated IDA patients within 3 to 6 months [5]. In a seminal randomized trial, eradication plus iron supplementation was superior to iron supplementation alone in achieving hemoglobin normalization at 12 months, confirming the independent contribution of H. pylori to iron depletion [5].

Diagnosis and Management

H. pylori diagnosis in the context of IDA should precede initiation of iron supplementation where possible, as iron therapy may transiently suppress bacterial density and reduce test sensitivity [7]. The urea breath test (UBT) and stool antigen test (HpSA) are the preferred non-invasive diagnostic methods, with sensitivity and specificity exceeding 90% when performed off PPI therapy for at least 2 weeks [7]. Upper endoscopy with antral and corpus biopsies (rapid urease test or histology) is indicated when there is clinical suspicion of peptic ulceration, atrophic gastritis, or mucosal neoplasia [6,7].

Eradication is recommended with standard first-line triple therapy (amoxicillin, clarithromycin, and PPI for 14 days) or bismuth-based quadruple therapy in areas with clarithromycin resistance above 15% [7]. Eradication should be confirmed by UBT or stool antigen test at least 4 weeks after antibiotic completion [7]. In patients with persistent IDA after confirmed eradication, oral or IV iron supplementation is required [1,20,21].

Pernicious Anemia and Autoimmune Atrophic Gastritis

Pathophysiology of Iron Deficiency in Biermer Disease

Pernicious anemia (PA) — the eponymous designation of autoimmune gastritis originally described by Biermer in 1872 — results from autoimmune destruction of gastric parietal cells mediated by anti-parietal cell antibodies (APCA) and anti-intrinsic factor antibodies (anti-IFA). The resulting autoimmune atrophic gastritis (AAG), characterized by loss of oxyntic glands with parietal and chief cell replacement by intestinal and pseudopyloric metaplasia, produces two clinically and biochemically interrelated deficiencies: vitamin B12 deficiency (through intrinsic factor loss) and iron deficiency (through achlorhydria) [6,7].

The mechanism of iron deficiency in AAG is primarily achlorhydria-mediated. Gastric acid serves two essential functions in non-heme iron bioavailability: it solubilizes insoluble ferric iron complexes from food matrices and creates the low-pH environment required for duodenal cytochrome b (DcytB)-mediated reduction of Fe^{3+} to Fe^{2+} at the duodenal brush border [1,6]. In the absence of acid (gastric pH >6 in achlorhydric patients), dietary non-heme iron remains in its ferric, oxidized, insoluble form and cannot be absorbed by divalent metal transporter 1 (DMT1) [1]. Heme iron absorption is less pH-dependent and is therefore relatively preserved in AAG, providing partial compensation in meat-eating patients.

Clinically, iron deficiency is often the earliest manifestation of AAG and may precede vitamin B12 (cobalamin) deficiency by several years. It is frequently diagnosed in younger patients, particularly women of childbearing age, where it may present as isolated IDA or even isolated biochemical iron deficiency. This early presentation can delay recognition of AAG, especially in the absence of macrocytosis or other signs of cobalamin deficiency [6,7].

The diagnostic challenge of combined vitamin B12 and iron deficiency in AAG is the so-called “masking phenomenon”: vitamin B12 deficiency produces macrocytic erythropoiesis (elevated MCV), while iron deficiency produces microcytic erythropoiesis (reduced MCV). In patients with both deficiencies, these opposing effects may cancel, producing a dimorphic blood film with normal MCV — a normocytic anemia that does not trigger the standard microcytic diagnostic reflex. Red cell distribution width (RDW) is typically markedly elevated (>16%) and is an important diagnostic clue [1]. Examination of the peripheral blood film showing a mixture of microcytic hypochromic and macrocytic red cells confirms the diagnosis.

Simultaneous measurement of serum ferritin and vitamin B12 (with functional markers such as methylmalonic acid, total homocysteine, or holotranscobalamin) is mandatory in all patients with suspected AAG [1].

Gastric Neuroendocrine Tumors and Hypergastrinemia

A clinically important complication of long-standing autoimmune atrophic gastritis (AAG) is the development of gastric type I neuroendocrine tumors (NETs), which arise from enterochromaffin-like (ECL) cell hyperplasia driven by hypergastrinemia, a compensatory response to achlorhydria [6,7]. Elevated fasting serum gastrin (>100 pg/mL) and chromogranin A are biomarkers of active oxyntic atrophy and should be measured in all patients with AAG [6,7].

In addition to NETs, AAG is associated with an increased risk of gastric adenocarcinoma, particularly the intestinal type, through the well-established Correa cascade, progressing from chronic atrophic gastritis to intestinal metaplasia, dysplasia, and eventually carcinoma [6]. This risk is further influenced by factors such as persistent inflammation, extent of atrophy, and, in some cases, coexisting H. pylori infection [4,6,7].

Endoscopic surveillance with systematic gastric mapping biopsies is recommended every 3 to 5 years to detect dysplasia, gastric intestinal metaplasia, early adenocarcinoma, and NET development [6]. Particular attention should be paid to the extent and severity of atrophy and metaplastic changes, which are key determinants of neoplastic risk.

Overall, patients with AAG require long-term follow-up combining biochemical monitoring and endoscopic surveillance to enable early detection of both neuroendocrine and epithelial gastric neoplasms.

Tea Consumption and Dietary Polyphenol-Mediated Iron Inhibition

Mechanism of Inhibition

Dietary polyphenols — a structurally diverse class of plant secondary metabolites abundant in tea, coffee, red wine, cocoa, and legumes — are among the most potent known inhibitors of non-heme iron absorption [8,9]. The principal bioactive compounds responsible for iron chelation in tea are condensed tannins (proanthocyanidins) and hydrolyzable tannins (including tannic acid), which form highly stable, insoluble ferric–tannate complexes in the intestinal lumen at physiological pH [9]. A single cup of black tea (200 mL, 2 g dry tea leaves) reduces non-heme iron absorption by 60 to 75% when consumed

simultaneously with an iron-containing meal, a magnitude of inhibition exceeding that of phytates and oxalates combined [9]. Green tea polyphenols (epigallocatechin gallate, EGCG) demonstrate comparable inhibitory potency [8,9].

The inhibitory effect is dose-dependent and maximal when tea is consumed with meals or within 30 minutes before or after ingestion. Caffeine content does not contribute to iron inhibition: decaffeinated black tea produces equivalent suppression of absorption [8,9]. Ascorbic acid (vitamin C) partially counteracts polyphenol-mediated inhibition by reducing Fe^{3+} to Fe^{2+} and competing for polyphenol binding, providing the physiological basis for the clinical recommendation to take oral iron supplements with vitamin C–rich beverages such as orange juice [1,8].

Clinical Impact and Epidemiological Evidence

The clinical relevance of habitual tea consumption as a contributing cause of IDA is supported by epidemiological and interventional evidence across multiple populations [8,9]. In South Asian women — who consume multiple cups of strong tea daily, frequently with meals — tea drinking is an independent risk factor for IDA after adjustment for menstrual blood loss, dietary iron intake, and socioeconomic status [8]. A meta-analysis demonstrated a statistically significant inverse association between tea consumption and iron status across 17 studies [8].

In clinical practice, tea-associated IDA should be suspected when iron deficiency occurs in a patient with apparently adequate dietary iron intake; when the patient is a habitual consumer of three or more cups of tea per day, particularly with meals; when standard investigation has excluded hemorrhagic, malabsorptive, and inflammatory causes; and when the response to oral iron supplementation is suboptimal despite adequate dosing [1,8].

The correction of iron absorption timing — separating iron supplement intake from tea consumption by at least 1 to 2 hours — and dietary counseling to substitute tea with water or vitamin C–rich fruit juice at mealtimes are the primary interventions, often sufficient to resolve iron deficiency when combined with standard oral iron therapy [1,8,9].

Pica and Pagophagia

Definition and Classification

Pica is defined as the persistent ingestion of non-nutritive, non-food substances for at least one month in individuals for whom such behavior is developmentally inappropriate. The phenomenon encompasses a broad spectrum of compulsive ingestion behaviors named according to the ingested material: pagophagia (ice), geophagia (soil, clay, or dirt), amylophagia (laundry starch or cornstarch), lithophagia (stones or gravel), and trichophagia (hair), among others.

Pagophagia — the compulsive craving and consumption of large quantities of ice — is the most prevalent form of pica in adults with IDA and is considered particularly characteristic of iron depletion states [10,11]. Its clinical relevance lies in its strong temporal association with iron status: it often resolves rapidly, typically within days to weeks, following iron repletion, making it a useful behavioral marker of treatment response [10,11].

Pathophysiology: Cause or Consequence?

The relationship between pica and iron deficiency is bidirectional and complex. On one hand, pica behaviors — particularly geophagia and amylophagia — are mechanistically capable of causing or exacerbating iron deficiency. Clay and soil contain abundant binding materials (notably montmorillonite and kaolin) that form stable complexes with dietary iron, zinc, and calcium in the intestinal lumen, thereby reducing their bioavailability. Experimental and metabolic balance studies have demonstrated that clay ingestion can reduce non-heme iron absorption by approximately 50 to 75%. Similarly, amylophagia (laundry starch ingestion) promotes the formation of viscous intraluminal gels that may reduce intestinal transit efficiency and decrease mucosal contact time for iron absorption. In addition, chronic clay ingestion may introduce heavy metals — particularly lead — and increase exposure to soil-borne pathogens, thereby adding toxicological and infectious contributors to anemia [10,11].

On the other hand, pagophagia in particular is consistently observed as a consequence rather than a cause of iron deficiency. The craving for ice is a specific but incompletely understood neurobehavioral manifestation of iron depletion, potentially related to the role of iron in dopaminergic neurotransmission and central thermoregulatory pathways. Its clinical value as a diagnostic clue in IDA has been recognized since Coltman's seminal report in 1969 [10]. The mechanism remains speculative; however, ice chewing in pagophagic patients with IDA has been proposed to transiently enhance alertness and cognitive performance, possibly via increased sympathetic activation and improved cerebral perfusion, suggesting a compensatory neurophysiological response to iron deficiency [10,11].

Diagnosis and Management

Pica should be actively inquired about in all patients presenting with IDA, as patients frequently conceal or minimize these behaviors due to shame or fear of stigma. The clinical history should specifically explore craving or ingestion of ice in large quantities (pagophagia), clay, soil, starch, chalk, or other non-food substances [10,11]. Blood lead levels should be measured in patients with geophagia given the known contamination of certain soil types with lead and other heavy metals [11].

The severity of anemia often correlates with the severity of pica behaviors: hemoglobin levels below 8 g/dL and profoundly depleted iron stores (ferritin <5 µg/L) are frequently observed in severe pagophagia-associated iron deficiency states [1,10]. IV iron is the preferred therapeutic modality in this context given: (1) the severity of iron deficiency at presentation; (2) the potential for ongoing luminal iron binding if geophagia or amylophagia persists during oral iron therapy; and (3) the rapid resolution of pagophagia symptoms — often within 24 to 48 hours after IV iron administration — which provides immediate symptomatic relief and reinforces treatment adherence [1,20].

Behavioral therapy, and in pediatric cases multidisciplinary management involving psychology and occupational therapy, are important to address the behavioral component of pica and reduce recurrence risk [11].

Heyde Syndrome

Pathophysiology: The Coagulopathy of Aortic Stenosis

Heyde syndrome, first described by Edward Heyde in 1958 as the association of calcific aortic stenosis with gastrointestinal bleeding from angiodysplasias, is now mechanistically understood as an acquired coagulopathy mediated by high-shear-stress–induced proteolysis of von Willebrand factor (vWF) [12,13]. In patients with severe aortic stenosis, the high-velocity turbulent transvalvular flow generates shear

stress that selectively unfolds ultra-large vWF multimers, exposing cryptic cleavage sites for ADAMTS13, the vWF-cleaving metalloprotease. Consequently, the largest and most hemostatically active vWF multimers — essential for platelet adhesion to injured endothelium — are selectively depleted, producing an acquired von Willebrand syndrome (type 2A) characterized by loss of high-molecular-weight multimers with relatively preserved total vWF antigen levels [13].

The resulting platelet dysfunction specifically impairs primary hemostasis at sites of microvascular injury — particularly intestinal angioectasias, which are common in elderly patients with calcific aortic stenosis [13,14]. The coincidence of these two age-related conditions produces a clinically significant synergistic bleeding phenotype: angioectasias that would otherwise bleed minimally become sites of recurrent, clinically important hemorrhage in the context of acquired vWF deficiency. The resulting blood loss is typically slow, intermittent, and occult, leading to IDA with minimal or absent overt gastrointestinal bleeding, which explains frequent diagnostic delay or misattribution to other etiologies [13,14].

Diagnosis

Heyde syndrome should be suspected in any elderly patient presenting with unexplained IDA or recurrent gastrointestinal bleeding in the context of calcific aortic stenosis, particularly when video capsule endoscopy (VCE) identifies small-bowel angioectasias [13,14]. The diagnostic confirmation relies on von Willebrand factor (vWF) multimer analysis demonstrating a selective loss of high-molecular-weight multimers with normal or only mildly reduced total vWF antigen levels, a pattern reflecting an acquired rather than congenital defect [13].

This profile is typically distinguished from hereditary type 2A von Willebrand disease by the clinical context (absence of lifelong bleeding history) and by preserved or near-normal factor VIII coagulant activity and vWF antigen levels [13]. A reduced ristocetin cofactor activity to vWF antigen ratio (vWF:RCo/vWF:Ag < 0.7) supports the diagnosis of an acquired functional vWF defect [13]. Transthoracic echocardiography is essential to quantify aortic stenosis severity (valve area, mean transvalvular gradient, peak velocity) and to guide the timing of valve intervention, which is the definitive treatment of the underlying hemodynamic trigger [14].

ADAMTS13 activity is typically normal, reflecting the shear-stress–dependent proteolysis of vWF multimers rather than autoimmune inhibition or thrombotic microangiopathy [13].

Management

The definitive treatment of Heyde syndrome is relief of left ventricular outflow tract obstruction through surgical aortic valve replacement (SAVR) or transcatheter aortic valve implantation (TAVI), which normalizes transvalvular flow dynamics, eliminates pathological shear stress, and allows rapid reconstitution of ultra-large von Willebrand factor (vWF) multimers within hours to days after correction of the valvular lesion [13,14].

Multiple observational studies and registry data have shown that successful TAVI is associated with a marked reduction in recurrent gastrointestinal bleeding and transfusion requirements, with reported decreases exceeding 80% in appropriately selected patients with Heyde syndrome and accessible bleeding lesions [14]. Restoration of vWF multimer distribution after valve replacement provides a mechanistic explanation for this clinical benefit, supporting the causal role of shear-stress–induced acquired von Willebrand syndrome in disease pathogenesis [13,14].

IV iron therapy plays a key supportive role as a bridge to definitive valve intervention, correcting IDA and optimizing perioperative hemoglobin levels in patients with chronic or recurrent blood loss [1,20]. Endoscopic therapy, particularly argon plasma coagulation of accessible angioectasias, may provide additional hemostatic control before valve intervention or as an adjunct strategy in patients with persistent or recurrent bleeding [13].

Hereditary Hemorrhagic Telangiectasia (Rendu-Osler-Weber Disease)

Genetic Basis and Pathophysiology

Hereditary hemorrhagic telangiectasia (HHT), also known as Rendu–Osler–Weber disease, is an autosomal dominant vascular dysplasia caused by loss-of-function mutations in genes encoding key components of the transforming growth factor-beta (TGF-β)/bone morphogenetic protein (BMP) signaling pathway in vascular endothelial cells [15]. The two major causative genes are ENG (endoglin, chromosome 9q34), responsible for HHT type 1, and ACVRL1 (activin A receptor-like kinase 1, chromosome 12q13), responsible for HHT type 2. Mutations in SMAD4 cause a combined syndrome of HHT and juvenile polyposis [15]. Genotype–phenotype correlations are clinically relevant: ENG mutations are associated with a higher prevalence of pulmonary arteriovenous malformations (PAVMs), with increased risk of paradoxical embolism and cerebral abscess, whereas ACVRL1 mutations are more frequently associated with hepatic AVMs and high-output cardiac failure [15].

The fundamental vascular lesion in HHT is the telangiectasia — a focal dilatation of post-capillary venules directly connected to arterioles without an intervening capillary bed, forming a fragile arteriovenous junction prone to spontaneous rupture [15]. The distribution of telangiectasias is characteristic and clinically useful: nasal mucosa (epistaxis in >90–95% of patients, often the presenting symptom), lips, oral cavity, fingertips, tongue, and gastrointestinal mucosa (particularly stomach, duodenum, and jejunum) [15].

Vascular endothelial growth factor (VEGF) plays a central role in the pathogenesis of HHT vascular lesions, reflecting dysregulated angiogenesis downstream of the TGF-β/BMP pathway. This mechanistic rationale underpins the therapeutic use of anti-angiogenic strategies such as bevacizumab in selected patients with severe bleeding or high-output cardiac failure [16].

Clinical Presentation and Iron Deficiency

The dominant hematological consequence of HHT is chronic IDA resulting from cumulative blood loss secondary to epistaxis and gastrointestinal telangiectasias. The pattern of gastrointestinal bleeding in HHT is typically chronic, occult, or micro-hemorrhagic: individual telangiectasias bleed slowly and intermittently, often below the threshold of visible hematochezia or melena, but the aggregate blood loss from multiple lesions over months to years results in clinically significant IDA, with ferritin values frequently <5 µg/L and hemoglobin levels <8 g/dL in advanced disease [15].

Epistaxis severity correlates imperfectly with gastrointestinal bleeding burden; some patients experience relatively mild nasal bleeding while sustaining the majority of their chronic blood

loss from gastrointestinal telangiectasias, particularly in the stomach and small bowel [15]. This dissociation contributes to diagnostic delay and underestimation of total bleeding burden.

The diagnosis of HHT is established clinically using the Curaçao criteria: (1) spontaneous recurrent epistaxis, (2) mucocutaneous telangiectasias at characteristic sites, (3) visceral arteriovenous malformations (pulmonary, hepatic, cerebral, spinal), and (4) a first-degree relative with confirmed HHT. Three or more criteria establish a definite diagnosis, two criteria make the diagnosis possible or suspected, and one criterion is considered unlikely in isolation [15]. Genetic testing (sequencing of ENG, ACVRL1, and SMAD4) confirms the diagnosis and enables cascade screening of at-risk relatives [15].

Investigation of Gastrointestinal Involvement

Video capsule endoscopy (VCE) is the recommended modality for characterizing the extent and distribution of small-bowel telangiectasias in HHT, with diagnostic yields exceeding 80% in symptomatic patients [15]. It provides a non-invasive, full-length assessment of the small intestine and is particularly useful for identifying the cumulative burden of mucosal lesions responsible for chronic occult bleeding.

Push enteroscopy allows evaluation and endoscopic treatment of proximal small-bowel lesions, particularly in the duodenum and proximal jejunum, where telangiectasias are frequently clustered [15]. Device-assisted enteroscopy (single- or double-balloon enteroscopy) is indicated for both diagnosis and therapeutic intervention when lesions are located beyond the reach of standard push enteroscopy, enabling targeted treatment of deeper jejunal and ileal angioectasias [15].

Upper gastrointestinal endoscopy frequently reveals gastric and duodenal telangiectasias, which are amenable to argon plasma coagulation (APC) ablation in cases of clinically significant bleeding or IDA [15].

Cross-sectional imaging with CT angiography and transthoracic contrast echocardiography are mandatory at diagnosis to screen for and characterize pulmonary arteriovenous malformations (PAVMs), while hepatic vascular malformations are best assessed using Doppler ultrasound, CT, or MRI depending on local expertise [15]. These evaluations are essential given the risk of paradoxical embolism, brain abscess, and high-output cardiac failure associated with visceral AVMs.

Management

The management of HHT-associated IDA is inherently multidisciplinary and must be individualized according to the predominant bleeding phenotype, lesion accessibility, and feasibility of pharmacological modulation of angiogenesis. IV iron replacement — most commonly ferric carboxymaltose or ferric derisomaltose administered intermittently (typically every 8 to 12 weeks, adjusted to iron indices and hemoglobin response) — remains the cornerstone of hematological management in patients with ongoing blood loss from lesions not amenable to complete endoscopic or interventional ablation [1,16]. Scheduled IV iron therapy can maintain hemoglobin above 10 g/dL in many patients and substantially reduce transfusion dependence, particularly when combined with lesion-directed therapy [1].

Anti-angiogenic therapy with bevacizumab (Avastin®, a recombinant humanized anti-VEGF monoclonal antibody administered intravenously, commonly at 5 mg/kg every 2 weeks for induction followed by maintenance regimens) has demonstrated clinically meaningful reductions in transfusion requirements and improvement in hemoglobin levels in observational studies and phase II trials of patients with severe HHT-related bleeding [16]. Dupuis-Girod et al. reported significant benefit in patients with severe hepatic vascular malformations and high-output cardiac failure [16]. More recent prospective data, including randomized evaluations of anti-VEGF strategies, support reductions in epistaxis severity and secondary improvements in gastrointestinal blood loss and anemia control [16].

Adverse effects of bevacizumab include hypertension, proteinuria, impaired wound healing, and rare arterial thromboembolic events, necessitating careful patient selection and monitoring [16]. Hormonal therapies such as estrogen-progestin combinations and antifibrinolytics such as tranexamic acid may provide modest benefit, particularly for epistaxis, but have limited and less consistent efficacy in gastrointestinal bleeding [15]. Thalidomide and lenalidomide, through anti-angiogenic and immunomodulatory mechanisms, have been used in refractory cases of HHT-related gastrointestinal bleeding, although their use is limited by neuropathy, thrombotic risk, and teratogenicity [15].

Additional Non-Hemorrhagic Digestive Causes

Autoimmune Inflammatory Enteropathy

Autoimmune enteropathy (AIE) is a rare immune-mediated disorder characterized by severe small intestinal mucosal injury with villous atrophy that is not responsive to a gluten-free diet, and is associated with circulating anti-enterocyte and anti-goblet cell antibodies. Clinically, AIE may present with IDA that is indistinguishable from celiac disease at presentation, both symptomatically and histologically. However, key discriminating features include negative anti-tissue transglutaminase IgA (anti-tTG IgA), persistence or progression of villous atrophy despite strict gluten-free diet adherence, and the detection of anti-enterocyte antibodies, which support the diagnosis of AIE over celiac disease [2,22].

From a pathophysiological standpoint, chronic immune-mediated epithelial injury leads to loss of absorptive surface area in the proximal small bowel, resulting in impaired iron uptake via DMT1-dependent pathways and clinically significant IDA [1]. Unlike celiac disease, mucosal damage in AIE is driven by a primary dysregulated immune response rather than gluten exposure, and therefore does not improve with dietary withdrawal.

Management requires systemic immunosuppression, most commonly with corticosteroids as first-line therapy, followed by steroid-sparing agents such as azathioprine. In refractory cases, biologic therapies including infliximab or locally acting corticosteroids such as budesonide have been used in selected patients, although evidence remains limited due to disease rarity. IV iron repletion is frequently required to correct IDA, particularly in the setting of severe malabsorption or active inflammatory disease [1,20].

Post-Bariatric Surgery and Post-Gastrectomy States

Surgical procedures that bypass or remove the stomach and proximal duodenum — including Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy with subsequent re-routing procedures, and Billroth II gastrectomy — produce IDA through multiple compounding mechanisms: reduced gastric acid secretion impairing ferric (Fe^{3+}) to ferrous (Fe^{2+}) iron reduction, exclusion of the duodenum (the principal site of non-heme iron

absorption), reduced dietary iron intake due to decreased gastric reservoir capacity, and accelerated gastric emptying limiting iron–mucosa contact time [1,20,21]. IDA affects approximately 20–50% of patients after RYGB within 2 years in the absence of systematic supplementation [20,21].

Oral iron absorption in this population is typically reduced to below 5–10% of ingested dose due to both anatomical exclusion and impaired luminal chemistry, making oral replacement frequently insufficient. IV iron — particularly high-dose single-infusion formulations such as ferric derisomaltose or ferric carboxymaltose — is therefore the preferred strategy for repletion and maintenance in patients with established deficiency or poor oral response [20,21]. Biannual or periodic IV iron infusions are often required for long-term maintenance depending on ongoing losses and dietary intake [20].

In addition to iron, other micronutrient deficiencies are common and clinically relevant. Vitamin B12 (cobalamin) deficiency is frequent due to reduced intrinsic factor secretion and impaired gastric acid–dependent release of food-bound cobalamin, while folate, vitamin D, calcium, and fat-soluble vitamins may also be affected depending on the type of surgery. Systematic supplementation protocols with iron and vitamin B12 should therefore be anticipated and implemented proactively in all patients undergoing bariatric or upper gastrointestinal bypass procedures to prevent long-term hematological and neurological complications [20,21].

Chronic Proton Pump Inhibitor Use

Long-term PP) therapy, while producing less severe hypochlorhydria than autoimmune atrophic gastritis, has been associated in observational and prospective studies with a modest but statistically significant reduction in non-heme iron absorption and an increased risk of IDA. Meta-analyses and large cohort studies suggest an adjusted relative risk of approximately 1.5–2.0 for IDA among long-term PPI users, although the magnitude of effect varies depending on baseline iron stores and comorbid conditions [1,6].

The clinical relevance is most evident in individuals with marginal dietary iron intake, increased physiological requirements (such as pregnancy, growth, or chronic blood loss), or concomitant conditions affecting gastric physiology, including H. pylori infection or pre-existing atrophic gastritis [4,6,7]. The mechanism is primarily related to reduced gastric acidity, which impairs solubilization of ferric iron (Fe^{3+}) and its subsequent reduction to the absorbable ferrous (Fe^{2+}) form, thereby limiting duodenal uptake via DMT1-dependent pathways [1].

In selected patients without a strong ongoing indication for acid suppression, PPI deprescribing, dose reduction, or step-down therapy should be considered as part of the management strategy for IDA. This approach should be individualized, balancing gastrointestinal risk (e.g., ulcer disease, Barrett's esophagus, NSAID protection) against the contribution of hypochlorhydria to impaired iron absorption [1,6].

A similar physiological concern applies to vitamin B12 absorption, which depends on gastric acid–mediated release of food-bound cobalamin; long-term acid suppression may therefore also contribute to biochemical or clinical vitamin B12 deficiency in susceptible individuals [1].

Integrated Diagnostic Algorithm

The systematic evaluation of IDA without overt gastrointestinal hemorrhage should proceed through the following stepwise framework, applied after confirmation of IDA (ferritin <30 µg/L, or <100 µg/L with transferrin saturation <20% in inflammatory states) and exclusion of hemorrhagic sources by adequate bidirectional endoscopy [1,2]:

1. **Step 1** — Dietary and behavioral history: quantify tea, coffee, and red wine consumption (timing relative to meals); screen for pica behaviors (ice, clay, starch); assess dietary iron intake (red meat, legumes, fortified cereals); evaluate vegetarian/vegan diet; identify PPI use [1].
2. **Step 2** — Autoimmune serological screening: anti-tTG IgA + total IgA (celiac disease); anti-parietal cell antibodies + anti-intrinsic factor antibodies (pernicious anemia / AAG); fasting gastrin + chromogranin A (achlorhydric atrophic gastritis) [1].
3. **Step 3** — H. pylori testing: urea breath test or stool antigen (off PPI for ≥2 weeks); if positive, eradicate and reassess iron status at 3 months before additional workup [2,4,7,20-22].
4. **Step 4** — Upper endoscopy with systematic biopsies: duodenal biopsies (4–6, including duodenal bulb) for Marsh grading; antrum + corpus biopsies (Sydney protocol) for H. pylori histology, intestinal metaplasia, and AAG mapping. In this context, video endoscopic capsule may be of interest and also discus by clinicians.
5. **Step 5** — Vitamin B12 / folate assessment: holotranscobalamin (active vitamin B12), serum vitamin B12, methylmalonic acid, total homocysteine, serum folate — mandatory in all patients with AAG or macrocytic component [1,6,8-11].
6. **Step 6** — Cardiovascular evaluation: echocardiography if calcific aortic stenosis is clinically suspected (ejection murmur, elderly patient, recurrent IDA); vWF multimer analysis if AvWS type IIA is suspected [1,18,19].
7. **Step 7** — HHT clinical criteria (Curaçao) and genetic testing: if epistaxis history, telangiectasias on examination, or family history; video capsule endoscopy for GI lesion mapping [1,20].
8. **Step 8** — Additional investigations guided by clinical context: Meckel's scan in patients <40 years; CT enterography if mass lesion suspected; blood lead level in geophagia; anti-enterocyte antibodies in seronegative villous atrophy [1,2].

Table 2. *Summary of Non-Hemorrhagic Digestive Causes of Iron Deficiency Anemia: Mechanism, Diagnosis, and Treatment.*

Cause	Mechanism of Iron Deficiency	Key Diagnostic Test(s)	Specific Treatment
Celiac disease	Duodenal/jejunal villous atrophy → malabsorption	Anti-tTG IgA + total IgA; duodenal biopsy (Marsh grade)	Strict gluten-free diet (GFD); IV iron if severe
H. pylori gastritis	Achlorhydria; iron sequestration; hepcidin upregulation; gastric mucosal iron uptake by bacteria	UBT; stool antigen; upper endoscopy + biopsy (CLO test)	Eradication therapy; iron supplementation if needed

Cause	Mechanism of Iron Deficiency	Key Diagnostic Test(s)	Specific Treatment
Pernicious anemia / Autoimmune atrophic gastritis (Biermer)	Achlorhydria → impaired Fe^{3+}→Fe^{2+} reduction; anti-IF Ab → B12 malabsorption (combined deficiency)	Anti-parietal cell Ab; anti-IF Ab; gastrin-17; chromogranin A; gastroscopy + biopsy	Vitamin B12 replacement (IM/SC); IV iron; PPI withdrawal if possible
Tea / polyphenol consumption	Dietary tannins form insoluble Fe^{3+}-tannate complexes → inhibit absorption	Dietary history; exclusion of other causes	Dietary counseling; timing iron intake away from tea/coffee
Pica / Pagophagia	Clay/starch/ice ingestion binds luminal iron; psychiatric/neurological comorbidity; reflects severe IDA	Clinical history; serum ferritin; exclude underlying cause; blood lead level	Treat underlying IDA (IV iron preferred); behavioral therapy
Heyde syndrome	Acquired vWF type IIA deficiency (shear-mediated proteolysis) → microvascular bleeding; angioectasias	vWF multimer analysis; aortic valve echocardiography; VCE	TAVI or AVR resolves vWF deficiency; APC for angioectasias
HHT (Rendu-Osler-Weber)	Multifocal mucocutaneous and GI telangiectasias → chronic occult blood loss; VEGF-driven angiogenesis	Clinical criteria (Curaçao); genetics (ENG, ACVRL1); VCE; CT pulmonary AVM	IV iron maintenance; bevacizumab; APC; estroprogestins
Autoimmune / inflammatory enteropathy	Villous atrophy; mucosal inflammation → malabsorption; hepcidin elevation → functional iron deficiency	Endoscopy + biopsy; anti-enterocyte Ab; IL-6; CRP; calprotectin	Immunosuppression; GFD (celiac); IV iron
Post-gastrectomy / bariatric surgery	Bypass of duodenum; achlorhydria; rapid gastric emptying → reduced contact time	History; ferritin; vitamin B12; folate; DEXA (bone density)	IV iron (oral poorly absorbed); lifelong supplementation protocol

anti-tTG IgA denotes anti-tissue transglutaminase IgA; UBT, urea breath test; HpSA, H. pylori stool antigen; APCA, anti-parietal cell antibodies; anti-IFA, anti-intrinsic factor antibodies; VCE, video capsule endoscopy; TAVI, transcatheter aortic valve implantation; AVR, aortic valve replacement; APC, argon plasma coagulation; vWF, von Willebrand factor; HHT, hereditary hemorrhagic telangiectasia; GFD, gluten-free diet.

Table 3. *Intravenous Iron Therapy by Clinical Scenario in Non-Hemorrhagic Digestive IDA.*

Clinical Scenario	Preferred Formulation	Dosing Strategy	Rationale
Active celiac disease on GFD — residual malabsorption	Ferric carboxymaltose or ferric derisomaltose	1000–1500 mg IV; repeat at 6–8 weeks if target Hb not reached	Intestinal absorption remains impaired despite GFD initiation; IV bypasses malabsorptive mucosa
H. pylori–associated IDA, post-eradication failure to normalize Hb	Ferric carboxymaltose	Single dose 1000 mg; reassess at 4 weeks	Eradication alone sufficient in ~50%; IV iron for remainder
Biermer disease / achlorhydric atrophic gastritis	Ferric carboxymaltose or ferric derisomaltose	Full calculated dose IV; combine with IM/SC hydroxocobalamin	Achlorhydria prevents ferric reduction; oral iron poorly absorbed
Severe pica (pagophagia) with Hb <8 g/dL	Ferric derisomaltose (single full-dose infusion)	Up to 20 mg/kg in single session	Rapid repletion; circumvents behavioral barrier to oral compliance; treats compulsion by resolving IDA
HHT with chronic recurrent GI blood loss	Ferric carboxymaltose or ferric derisomaltose	Scheduled infusions every 8–12 weeks; individualize frequency by Hb response	Continuous chronic loss requires maintenance; oral iron inadequate for ongoing hemorrhage rate
Heyde syndrome pre-TAVI/AVR	Ferric carboxymaltose	1000 mg IV; bridge to valve intervention	Pre-procedure optimization; post-AVR/TAVI discontinue once vWF normalizes
Post-Roux-en-Y gastric bypass	Ferric derisomaltose (preferred: single full-dose)	Annual or biannual full-dose IV iron	Duodenal bypass; achlorhydria; oral iron absorption <10%

IV denotes intravenous; GFD, gluten-free diet; Hb, hemoglobin; PPI, proton pump inhibitor; TAVI, transcatheter aortic valve implantation; AVR, aortic valve replacement; HHT, hereditary hemorrhagic telangiectasia; RYGB, Roux-en-Y gastric bypass. Ferric carboxymaltose: max 1000 mg/session. Ferric derisomaltose: up to 20 mg/kg as single dose. Note: ferric carboxymaltose associated with transient hypophosphatemia in 10–27% with repeated dosing; ferric derisomaltose preferred when multiple sessions anticipated.

Intravenous Iron Therapy in Non-Hemorrhagic Digestive IDA

IV iron is the cornerstone of iron deficiency anemia (IDA) management when the underlying gastrointestinal condition impairs oral iron absorption, when the severity of anemia requires rapid repletion, or when oral iron is poorly tolerated or ineffective despite adequate dosing. The indications for IV iron across the conditions reviewed in this article are summarized in Table 3. The physiological rationale for IV iron superiority is straightforward: by bypassing the gastrointestinal lumen and directly delivering iron to transferrin and reticuloendothelial storage pools, IV iron circumvents the major mechanisms responsible for oral iron failure—achlorhydria, mucosal malabsorption, competitive luminal inhibition, and inflammation-mediated iron restriction [1,20].

Ferric carboxymaltose (FCM; Ferinject®/Injectafer®) and ferric derisomaltose (FDI; Monofer®/Monoferric®) are the most widely used modern IV iron formulations. Ferric carboxymaltose, typically administered at doses up to 1000 mg per infusion over approximately 15 minutes (with repeat dosing after ≥7 days if required), has been extensively studied in heart failure, inflammatory bowel disease, postpartum anemia, and celiac disease–associated iron deficiency [18–21]. A clinically relevant adverse effect specific to ferric carboxymaltose is hypophosphatemia, mediated by fibroblast growth factor 23 (FGF23)–induced renal phosphate wasting. This occurs in approximately 10–27% of patients after repeated administration and may, in rare cases, lead to symptomatic osteomalacia [20].

Ferric derisomaltose allows administration of higher single doses (up to 20 mg/kg) and is associated with a lower risk of hypophosphatemia due to its different carbohydrate shell structure and pharmacokinetic profile, making it particularly advantageous when full iron deficit correction is desired in a single session [20,21].

Iron requirement estimation is commonly performed using the Ganzoni formula: Total iron deficit (mg) = body weight (kg) × (target Hb − actual Hb in g/dL) × 2.4 + 500 mg (iron stores). For example, in a 70 kg patient with hemoglobin 7 g/dL and a target of 13 g/dL, the calculated deficit is approximately 1508 mg, typically requiring either two ferric carboxymaltose infusions or a single ferric derisomaltose administration.

Treatment response should be monitored using hemoglobin, reticulocyte count, ferritin, and transferrin saturation at approximately 4 and 12 weeks after infusion. In conditions characterized by ongoing chronic blood loss or persistent malabsorption—such as hereditary hemorrhagic telangiectasia, Heyde syndrome, or refractory celiac disease—scheduled maintenance IV iron therapy every 8 to 12 weeks may be required, with dosing individualized to maintain hemoglobin levels above 11–12 g/dL and ferritin above 50 µg/L, thereby preventing recurrent symptomatic anemia [1,15,20].

Special Populations

Elderly Patients

In elderly patients, iron deficiency anemia (IDA) of non-hemorrhagic gastrointestinal origin is frequently multifactorial. Several mechanisms commonly coexist and interact, including hypochlorhydria or achlorhydria (secondary to autoimmune gastritis/Biermer disease, H. pylori–associated corpus atrophic gastritis, or chronic PPI use), reduced dietary iron intake, impaired mucosal absorption due to small bowel disease or post-surgical anatomy, and chronic disease–related functional iron deficiency driven by inflammation and hepcidin-mediated iron sequestration [1,6,7].

This multifactorial context makes a systematic diagnostic approach essential. Empirical iron supplementation without etiological investigation is insufficient in this population, as it risks masking underlying treatable conditions such as celiac disease, autoimmune gastritis, or occult systemic inflammatory disease, and may delay targeted therapy or surveillance for gastric neoplasia in high-risk settings [2,6]. A structured evaluation integrating gastrointestinal, nutritional, pharmacological, and inflammatory causes is therefore required in all older adults presenting with IDA without overt bleeding.

IV iron plays a particularly important role in elderly patients. Oral iron is frequently limited by gastrointestinal intolerance (notably constipation, nausea, and abdominal discomfort), reduced adherence, and clinically relevant drug–drug or drug–food interactions (including calcium, antacids, and polypharmacy-related timing issues). In addition, age-related reductions in gastric acidity and comorbid conditions further impair oral iron bioavailability. IV iron therefore provides a more reliable and rapid method of repletion in this population, particularly when rapid correction of anemia is required or when oral therapy has failed or is not tolerated [20,21]..

Patients with Coexisting Vitamin B12 or Vitamin B9 Deficiency

Combined vitamin B12 and folate deficiencies are encountered in several clinical settings, including malabsorptive disorders (such as extensive celiac disease, post-bariatric surgery or gastrectomy states), malnutrition, and strict diets lacking animal-derived products. These deficiencies require simultaneous correction to ensure complete hematologic recovery and to avoid diagnostic and therapeutic pitfalls [1,2].

This association has important diagnostic implications, as the opposing effects on red blood cell indices may mask typical findings. Vitamin B12 and/or folate deficiency classically cause macrocytosis; however, coexisting conditions such as iron deficiency, chronic inflammation, or mixed nutritional deficiencies may attenuate the increase in mean corpuscular volume (MCV), resulting in a normocytic or only mildly altered presentation. In this context, red cell distribution width (RDW) is often markedly elevated, reflecting significant anisocytosis with mixed red cell populations and increased heterogeneity of erythrocyte size [1,3].

The peripheral blood smear may show a dimorphic pattern, with coexistence of macro-ovalocytes, hypochromic microcytes, and other abnormalities of erythroid maturation. This finding should prompt systematic evaluation of both vitamin B12 and folate status rather than a sequential or single-deficiency approach, particularly in patients with malabsorption or complex nutritional risk profiles [1,3].

A key physiological concept is the “unmasking effect” during treatment. Isolated correction of either vitamin B12 or folate deficiency can lead to a rapid increase in effective erythropoiesis, thereby increasing substrate demand and revealing a previously unrecognized coexisting deficiency. Conversely, treating only one deficiency may result in partial hematologic recovery without full biochemical or clinical normalization, delaying definitive diagnosis and appropriate combined supplementation [1].

For these reasons, concurrent replacement of vitamin B12

and folate is recommended when dual deficiency is suspected or confirmed. Monitoring should include serial hemoglobin, MCV, RDW, as well as serum vitamin B12 and folate levels, or functional biomarkers such as homocysteine (elevated in both deficiencies) and methylmalonic acid (specific for vitamin B12 deficiency), to ensure complete and sustained correction [1,2].

Pregnancy

Pregnant women with celiac disease, autoimmune atrophic gastritis, or a history of bariatric surgery are at particularly high risk of severe iron deficiency anemia (IDA), due to the additive effects of increased physiological iron requirements (expanding maternal red cell mass, placental–fetal iron transfer) and impaired intestinal absorption. These conditions frequently coexist with reduced gastric acidity, proximal small bowel malabsorption, or surgically altered anatomy, resulting in limited efficacy of oral iron supplementation and a higher likelihood of refractory anemia [1,2,20].

IV iron is safe and effective during the second and third trimesters of pregnancy and is recommended when oral iron fails to achieve an adequate hematologic response, is poorly tolerated, or when rapid correction is clinically indicated (e.g., moderate-to-severe anemia late in gestation). Among available formulations, ferric carboxymaltose and iron sucrose have the most extensive safety and efficacy data in pregnancy, demonstrating effective hemoglobin correction with acceptable maternal and fetal safety profiles [20,21]. IV iron also provides the advantage of ensuring repletion in states of impaired absorption, which are common in the aforementioned high-risk conditions.

In contrast, H. pylori eradication during pregnancy is generally deferred to the postpartum period in most clinical settings, given the limited safety data and the need for combination antibiotic regimens that may include agents with potential fetal risk. Management during pregnancy therefore focuses primarily on iron repletion and stabilization rather than definitive eradication therapy [4,7].

Future Directions

Several emerging areas of investigation are likely to refine the diagnosis and management of non-hemorrhagic digestive iron deficiency anemia (IDA) over the coming decade.

Point-of-care hepcidin measurement, enabling rapid bedside discrimination between absolute iron deficiency and functional iron deficiency driven by inflammation, is under active clinical development. If validated, it may significantly improve the precision of IV iron dosing and timing compared with current ferritin- and transferrin saturation–based algorithms, particularly in complex conditions such as chronic inflammatory states and mixed nutritional deficiencies [1].

New oral iron formulations designed to improve bioavailability under conditions of elevated hepcidin, hypochlorhydria, or mucosal inflammation are also being investigated. Agents such as sucrosomial iron and ferric maltol have shown improved tolerability and encouraging absorption profiles in early studies involving patients with inflammatory bowel disease and celiac disease, suggesting a potential expansion of oral iron use in settings previously considered refractory to oral therapy [20,21].

In celiac disease, disease-modifying approaches beyond the gluten-free diet are in development, including gluten-degrading enzymes (endopeptidase combinations), modulators of intestinal permeability (tight junction regulators), and immunomodulatory strategies such as anti–IL-15 therapies for refractory disease. These interventions may accelerate mucosal healing and thereby improve recovery of duodenal iron absorption, reducing long-term dependence on IV iron in selected patients [2,22].

In hereditary hemorrhagic telangiectasia (HHT), ongoing

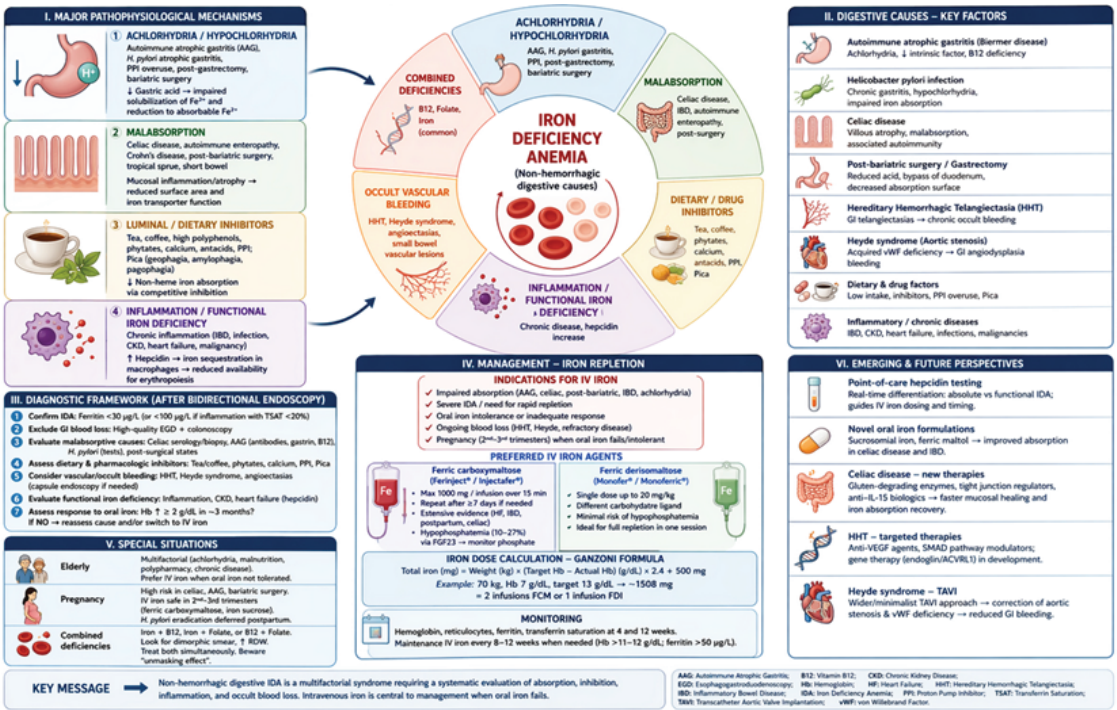

Figure. *Non-Hemorrhagic Digestive Cause of Iron Deficiency Anemia: Mechanism, Diagnostic and Management.*

phase III trials of anti-VEGF strategies and other angiogenesis-modulating agents, including approaches targeting TGF-β/BMP signaling pathways (e.g., SMAD pathway modulation), may offer more durable control of mucocutaneous and gastrointestinal bleeding. In the longer term, gene therapy approaches aiming at restoration of ENG or ACVRL1 function represent a potential disease-modifying strategy [15,16].

In Heyde syndrome, broader and earlier use of transcatheter aortic valve implantation (TAVI), including minimalist procedural strategies in frail elderly patients, is expected to substantially reduce the burden of recurrent gastrointestinal bleeding by correcting the underlying shear stress–induced acquired von Willebrand syndrome. This evolution in structural heart disease management is likely to further shift Heyde syndrome from a chronic bleeding disorder to a largely reversible condition in many patients [13,14].

Conclusions

Iron deficiency anemia presenting without overt gastrointestinal hemorrhage challenges the clinician to think beyond the endoscope and consider a rich spectrum of non-hemorrhagic digestive etiologies, each with a distinct pathophysiological mechanism, diagnostic signature, and therapeutic target. Celiac disease demands serological screening in all unexplained IDA cases. H. pylori eradication may itself resolve IDA. Pernicious anemia and autoimmune atrophic gastritis require combined vitamin B12 and iron repletion with parenteral pathways for both. Tea polyphenols are a correctable dietary inhibitor whose clinical significance is underestimated. Pica — and pagophagia in particular — is both a consequence and a perpetuating cause of iron deficiency that resolves dramatically with iron repletion. Heyde syndrome offers the remarkable prospect of complete hemostatic cure through aortic valve intervention. Hereditary hemorrhagic telangiectasia requires lifelong multidisciplinary management combining IV iron maintenance, endoscopic ablation, and emerging anti-angiogenic pharmacotherapy (Figure).

The unifying therapeutic message across all these conditions is that oral iron is frequently insufficient: the same digestive pathology that caused iron depletion also impairs its oral correction. IV iron — administered via modern high-dose, rapid-infusion formulations — is the therapeutic backbone that enables iron repletion while the underlying condition is being diagnosed and specifically treated. A systematic, etiologically driven approach to unexplained IDA, integrating the diagnostic algorithm proposed in this review, will reduce diagnostic delay, avoid unnecessary transfusion, and ensure that the treatable underlying condition receives the targeted intervention it requires.

Conflict of interest

Ihe authors declare no conflicts of interest related to this work.

Author contributions

- All authors contributed equally to the conception, drafting, critical revision, and final approval of the manuscript.
- Emmanuel Andrès: conceptualization, supervision, critical revision
- Jean-Edouard Terrade: drafting, literature review, critical revision
- Xavier Jannot: methodological input, data structuring, critical revision
- Edward Nasco: drafting, literature synthesis
- Marie Caroline Taquet: drafting, clinical input
- Marie Caroline Dalmas: literature review, clinical input
- Alpha Diallo: drafting, data synthesis
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