Iron deficiency anemia in inflammatory bowel disease

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Abstract

Anemia is a common extraintestinal manifestation of inflammatory bowel disease (IBD) and is frequently overlooked as a complication. Patients with IBD are commonly found to have iron deficiency anemia (IDA) secondary to chronic blood loss, and impaired iron absorption due to tissue inflammation. Patients with iron deficiency may not always manifest with signs and symptoms; so, hemoglobin levels in patients with IBD must be regularly monitored for earlier detection of anemia. IDA in IBD is associated with poor quality of life, necessitating prompt diagnosis and appropriate treatment. IDA is often associated with inflammation in patients with IBD. Thus, commonly used laboratory parameters are inadequate to diagnose IDA, and newer iron indices, such as reticulocyte hemoglobin content or percentage of hypochromic red cells or zinc protoporphyrin, are required to differentiate IDA from anemia of chronic disease. Oral iron preparations are available and are used in patients with mild disease activity. These preparations are inexpensive and convenient, but can produce gastrointestinal side effects, such as abdominal pain and diarrhea, that limit their use and patient compliance. These preparations are partly absorbed due to inflammation. Non-absorbed iron can be toxic and worsen IBD disease activity. Although cost-effective intravenous iron formulations are widely available and have improved safety profiles, physicians are reluctant to use them. We present a review of the pathophysiologic mechanisms of IDA in IBD, improved diagnostic and therapeutic strategies, efficacy, and safety of iron replacement in IBD.

Key words: Iron deficiency anemia; Inflammatory bowel disease; Hepcidin; Ferritin; Oral iron; Intravenous iron

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Core tip: Iron deficiency anemia (IDA) is increasingly recognized as a common complication in patients with inflammatory bowel disease (IBD). IDA has a significant impact on quality of life and health care costs. This comprehensive review article discusses the latest advances in understanding the pathophysiologic mechanisms involved in development of IDA in patients with IBD, and reviews new diagnostic tests and therapeutic options with high safety indexes for the management of IDA. This article aims at increasing physician awareness and understanding of the complex mechanisms involved in IDA, and the current cutting-edge approach for the management of IDA in patients with IBD.

INTRODUCTION

Inflammatory bowel disease (IBD) describes a set of chronic gastrointestinal illnesses, including Crohn's disease (CD) and ulcerative colitis (UC), of multifactorial etiology, which proceed with periods of relapse and remission. Extraintestinal complications are common in IBD, and are reported in more than 25% of patients[1]. Anemia is one of the most common manifestations of IBD[2]. One-third of patients with IBD have hemoglobin levels below 12 g/dL[3]. The anemic state is strongly correlated with quality of life, and is an important problem in the therapeutic management of patients with chronic disease[4].

ABSOLUTE AND FUNCTIONAL IRON DEFICIENCY

Most cases of anemia in patients with IBD result from functional or absolute iron deficiency. Functional iron deficiency is a state in which there is insufficient availability of iron for incorporation into erythroid precursors despite normal or increased body iron stores[5,6]. In patients with absolute iron deficiency, iron is stored in the bone marrow. Other parts of the monocyte-macrophage system in the liver and spleen become depleted, making iron unavailable for normal or increased rates of erythropoiesis. This may occur as the result of poor dietary intake of iron, reduced iron absorption, and/or increased blood loss.

SIGNS AND SYMPTOMS OF IRON DEFICIENCY ANEMIA

Signs and symptoms of iron deficiency depend on the severity and chronicity of the anemia, in addition to the usual signs of anemia, including fatigue, pallor, and reduced exercise capacity. Cheilosis and koilonychia are signs of advanced tissue iron deficiency which are not frequently seen in the modern world, due to early diagnosis and timely correction.

Key symptoms of anemia, such as dyspnea and tachycardia, are caused by decreased blood oxygen levels and peripheral hypoxia. Compensatory blood shifting from the mesenteric arteries may worsen perfusion of the intestinal mucosa[7]. Motility disorder, nausea, anorexia, and even malabsorption have been attributed to anemia. Reduced metabolic and energy efficiency during physical activity also contribute to weight loss in anemia[8].

Central hypoxia may lead to symptoms such as headache, dizziness, vertigo, or tinnitus. Several studies have confirmed that treatment of anemia improves cognitive function[9]. Iron is a component of hemoglobin myoglobin, cytochromes, and many other enzymes. Thus, anemia negatively impacts almost every aspect of daily life in patients with IBD. Men with iron deficiency anemia (IDA) may suffer from impotence. Loss of libido contributes to impaired quality of life in both sexes[10]. In addition, latent iron deficiency may be responsible for "non-hematological" symptoms such as hair loss, paresthesias of the hands and feet, and reduced cognitive function, and may also be significantly associated with restless leg syndrome.

CLINICAL RELEVANCE

Anemia and iron deficiency have a dramatic impact on patients' quality of life, yet anemia in patients with IBD is still underdiagnosed and undertreated. In the United States, annual emergency room visits for anemia average around 209000[11], drastically maximizing health care costs. In a patient population with the predisposition for anemia, like patients with IBD, early diagnosis and management of iron deficiency can promptly reduce hospital visits, improve quality of life, reduce loss of work, and, ultimately, lower health care costs.

CAUSES OF IRON DEFICIENCY ANEMIA IN IBD

Anemia in IBD patients involves multiple pathogenic mechanisms resulting in low hemoglobin levels and compromised quality of life. Although ongoing blood loss from chronically inflamed intestinal mucosa and micronutrient deficiency (iron and B12) are the main mechanisms underlying the development of anemia in patients with IBD, chronic inflammation, hemolysis, and medication-induced myelosuppression may also play important roles in both the development of anemia and the management of this condition[12,13]. Anemia of chronic disease (ACD) and IDA are the two most common causes of anemia in patients with IBD[14,15].

Table 1 Causes of anemia in inflammatory bowel disease

Common causes	Less common causes	Rare causes
Iron deficiency anemia	B12 deficiency	Hemolysis
Anemia of chronic inflammation	Folic acid deficiency	Chronic renal insufficiency
	Medications causing B12/Folate deficiency	Myelodysplastic syndrome
		Medication induced aplasia
		Congenital hemoglobinopathies
		Protein starvation
		Anemia in liver disease

Patients with IDA and concomitant ACD tend to have more severe anemia compared with patients with ACD alone[14]. Table 1 presents the causes of anemia in patients with IBD. Figure 1 outlines causes of IDA.

PATHOPHYSIOLOGY OF IRON DEFICIENCY ANEMIA IN IBD

Up to 3-4 g of iron is stored in the human body. Around 1-2 mg of iron is lost every day through desquamation of epithelial cells of the skin, gastrointestinal tract, bile ducts, and urinary tract, and through blood loss in menstruating women[16].

Iron homeostasis is strictly maintained by iron absorption from the duodenal enterocytes, and is tightly regulated by hepcidin (Figure 2). Hepcidin is a 25-amino-acid peptide hormone, has intrinsic antimicrobial activity, and is an acute-phase protein that is primarily synthesized by hepatocytes[17]. Cellular targets for hepcidin and iron-exporting cells are villous enterocytes, reticuloendothelial macrophages, and hepatocytes. Hepcidin binds to the basolateral transporter and iron exporter ferroportin 1, leading to its phosphorylation, internalization by binding to JAK 2, and lysosomal degradation, thus preventing iron release into the plasma[16]. Increased hepcidin levels downregulate ferroportin, thereby reducing iron efflux from the enterocytes and macrophages, causing hypoferremia. The increase in enterocyte iron content reduces the expression of enterocyte brush border reductase (Dcytb) and divalent metal transporter 1 (DMT1) on villous enterocytes, inhibiting dietary iron absorption causing iron deficiency anemia[18]. Therefore, by regulating the expression of DMT1 and ferroportin, hepcidin acts as a negative regulator of iron absorption in the duodenum and of iron release from the enterocytes and macrophages.

Hepcidin expression is upregulated by iron overload, infection, and inflammation, through proinflammatory cytokines such as interleukin (IL)-6 *via* the JAK 2 mediated STAT 3 signaling, thus limiting iron absorption[16,19]. Hepcidin expression is downregulated by hypoxia, oxidative stress, iron deficiency anemia, and ineffective erythropoiesis, thus increasing iron availability (Figure 2)[20].

Hepcidin expression is mediated by two signaling pathways that involve bone morphogenetic protein (BMP) and transferrin receptor 2 (TfR2; Figure 3). The BMP signaling pathway includes BMP 6, hemojuvelin (HJV), and SMAD4, which constitute the major signaling pathway for hepcidin expression; TfR2 and the hereditary hemochromatosis protein (HFE)-dependent signaling pathway modulate this response[21,22]. In high iron conditions, transferrin-iron in the plasma forms a complex with HFE and TfR2 to promote hepcidin expression[21]. In iron-deficient conditions, there is downregulation of TfR2 and upregulation of TfR1. HFE is sequestered by TfR1, preventing its interaction with TfR2, thereby downregulating hepcidin expression (Figure 3)[21,23].

DIAGNOSTIC WORK-UP OF IRON DEFICIENCY ANEMIA IN IBD

Healthcare providers screen for IDA by measuring hemoglobin, serum ferritin, and C-reactive protein (CRP). Based on expert opinion and common clinical practice, screening is recommended at least every 3 mo for outpatients with active disease, and once every 6 to 12 mo for patients in remission or with mild disease; screening is not applicable to hospitalized patients[24].

The World Health Organization (WHO) definitions of anemia also apply to patients with IBD. WHO defines anemia as hemoglobin levels < 13 g/dL (hematocrit < 39%) in males, < 12 g/dL (hematocrit < 36%) in nonpregnant females, and < 11 g/dL (hematocrit < 33%) in pregnant females[25]. Severe IDA is defined as hemoglobin levels < 10 g/dL.

If a patient meets WHO criteria for anemia, a basic anemia workup should be initiated to determine the cause of anemia. The basic workup includes serum ferritin, transferrin, transferrin saturation, and CRP levels. If the cause of anemia is unclear despite the results of the above workup, more extensive testing is recommended. Further tests include vitamin B12, folic acid, haptoglobin, lactate dehydrogenase, creatinine, and reticulocyte counts[24].

Both IDA and ACD often coexist with IBD, and the treatment for each differs. There is no single laboratory parameter that differentiates one from the other. Consequently, supplementary laboratory tests are required to differentiate IDA from ACD. These tests include soluble transferrin receptor, soluble transferrin receptor-ferritin index, reticulocyte hemoglobin concentration, zinc protoporphyrin, the percentage of hypochromic red cells, and hepcidin levels[16]. IDA in IBD is diagnosed based on a combination of factors, taking inflammation into account. The laboratory findings in IDA, ACD, mixed IDA, and ACD are shown in Table 2[16,22].

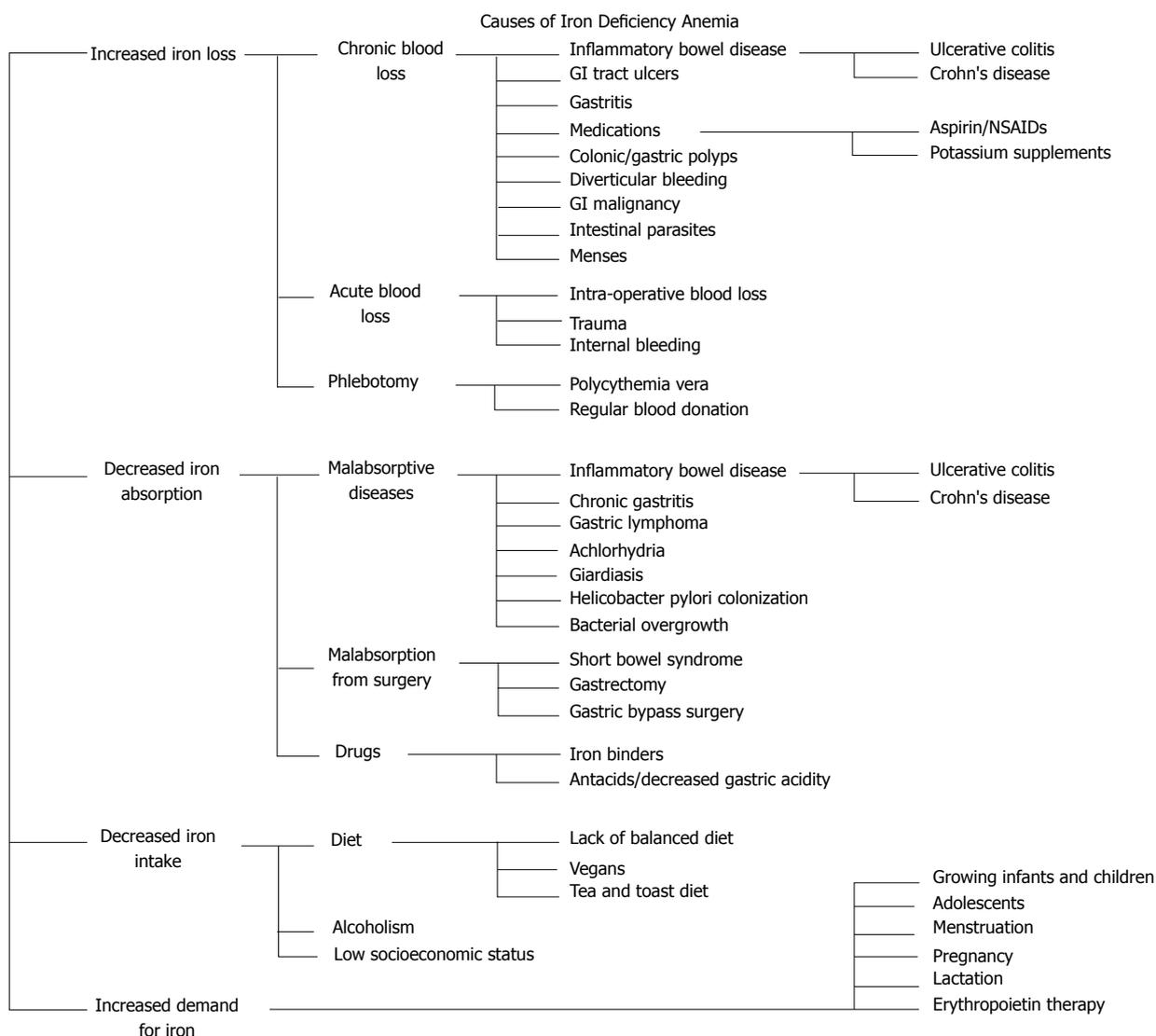Serum ferritin is a measure of stored iron content in the reticuloendothelial system; in absolute iron

Causes of Iron Deficiency Anemia

Figure 1 Causes of iron deficiency anemia. GI: Gastrointestinal; NSAIDs: Nonsteroidal anti-inflammatory drugs.

Table 2 Laboratory findings in iron deficiency anemia, anemia of chronic disease, mixed iron deficiency anem and anemia of chronic disease[16,31]			
Laboratory measures	**IDA**	**ACD**	**IDA and ACD**
Serum iron	↓	↓	↓
Hemoglobin	↓	↓	↓
MCV	↓	↓ or normal	↓ or normal
CRP	Normal	↑↑	↑
Serum ferritin	↓	↑	↑ or normal
Transferrin	↑	↓ or normal	↓
Transferrin saturation	↓	↓	↓
sTfR	↑	↓	↑ or normal
sTfR- Ferritin index	High (> 2)	Low (< 1)	High (> 2)
Reticulocyte Hb content (CHr, pg)	< 28	⩾ 28	< 28
Zinc protoporphyrin (μmol/mol heme)	> 40	< 40	> 40
Percentage of hypochromic RBC	> 5	< 5	> 5
Hepcidin	↓	↑	↑

↓: Low/decreases; ↑: High/increases; ↑↑: Very high; IDA: Iron deficiency anemia; ACD: Anemia of chronic disease; MCV: Mean corpuscular volume; CRP: C-reactive protein; sTfR: Soluble transferrin receptor; Hb: Hemoglobin; RBC: Red blood cell.

deficiency, the serum ferritin concentration is < 15 μg/L[16]. Serum ferritin is an acute-phase reactant; normal or high levels may be found in inflammatory conditions despite iron deficiency[26]. Therefore, the guidelines recommend that in patients with quiescent IBD without biochemical or clinical evidence of inflammation, iron deficiency is defined as serum ferritin < 30 g/L or transferrin saturation (TSAT) < 16%[24]. In the presence of active IBD with inflammation, as evidenced by elevated CRP, the guidelines give a cut-off level of serum ferritin < 100 g/L to increase sensitivity and specificity[24,27].

Microcytosis (low mean corpuscular volume, MCV) and hypochromia (low mean corpuscular hemoglobin, MCH), available from the complete blood count, are indicators of absolute iron deficiency. High MCV is found secondary to vitamin B12 and folate deficiency, the use of certain medications (thiopurines; azathioprine or 6-mercaptopurine), alcoholism, and hypothyroidism[24]. Therefore, normal or high MCV does not exclude IDA as a possibility. In patients with ACD, MCV may be low or
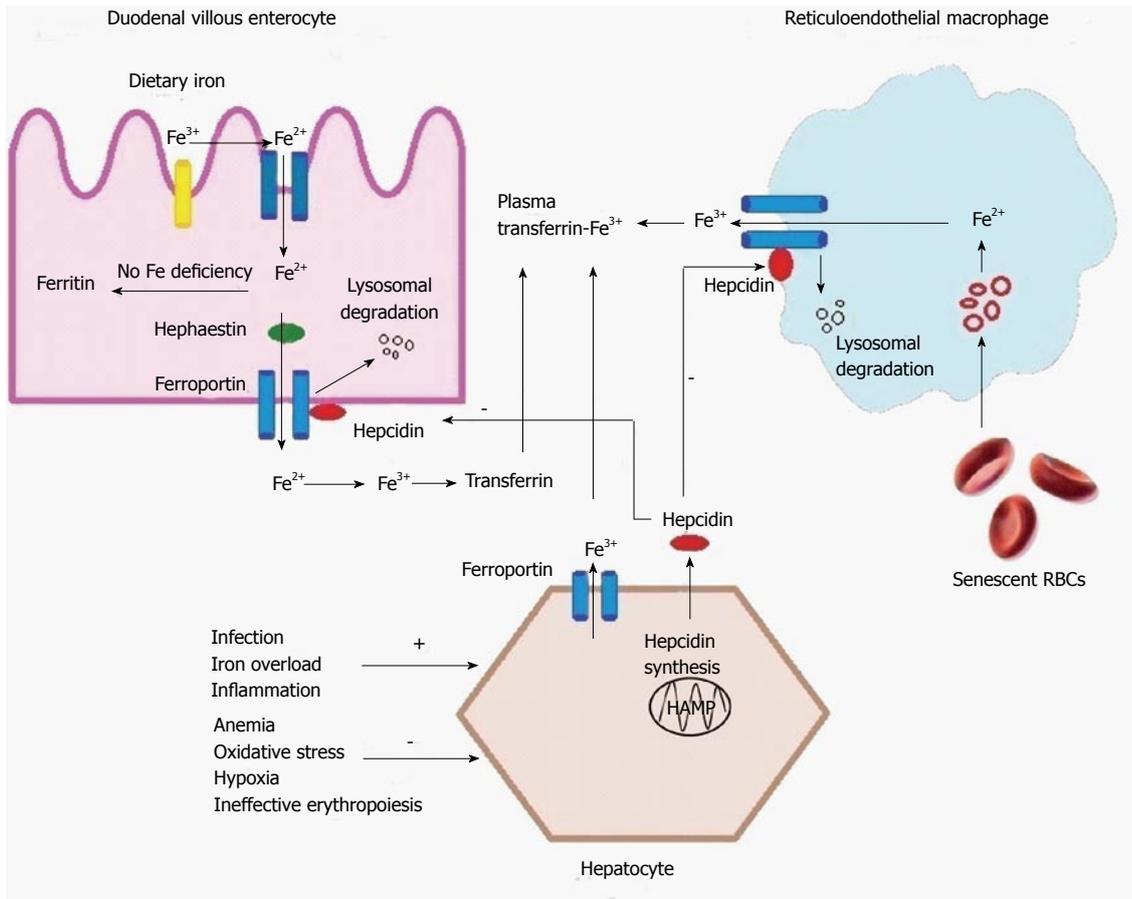
Figure 2 Role of hepcidin in the regulation of iron homeostasis. Fe^{3+} is reduced to Fe^{2+} by enterocyte brush border reductase Dcytb, transported across brush border membrane by DMT1. If iron demand is low, Fe^{2+} is stored as ferritin and sloughed with enterocytes. If iron demand is high, iron is oxidized by oxidase hephaestin and then exported into the plasma at the basolateral membrane by ferroportin[23]. Hepcidin binds to iron exporter, ferroportin 1, leading to its phosphorylation, internalization by binding to JAK 2 and lysosomal degradation, thus preventing iron release into the plasma[16]. DcytB: Duodenal ferric reductase; DMTI: Divalent metal transporter 1.
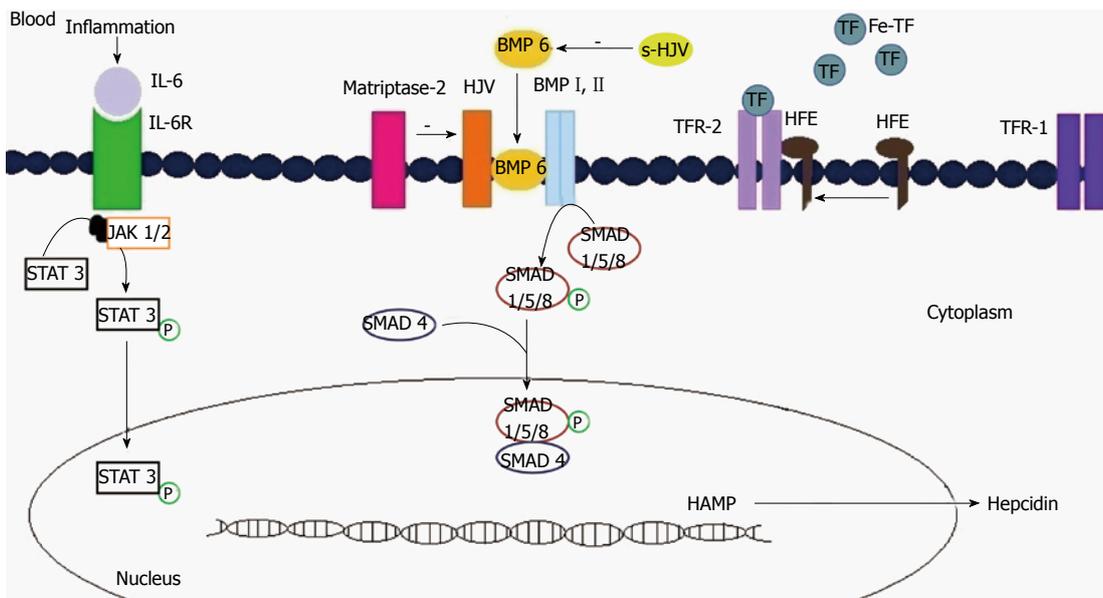
Figure 3 Signaling pathways regulating hepcidin expression in the liver. Enterocyte iron induces BMP6 expression. BMP6 is released *via* the portal vein to act on cell-surface receptors in the liver, BMPR-I, BMPR-II, and HJV, a co-receptor of BMP, leading to phosphorylation of cytosolic transcription factors, SMAD 1/5/8, which complex with SMAD 4[16,21]. This heteromeric complex translocates to the nucleus and enhances transcription of hepcidin gene, HAMP. In iron deficiency, HJV is cleaved by matriptase-2 activation reducing BMP signaling, and BMP is sequestered by s-HJV, preventing its interaction with plasma membrane HJV, decreasing hepcidin expression[21]. IL-6: Interleukin 6; BMP: Bone morphogenetic protein; HJV: Hemojuvelin; s-HJV: Soluble HJV; TfR2: Transferrin receptor 2; HFE: Hereditary hemochromatosis protein; BMPR: Bone morphogenetic protein receptors.

normal.

Serum transferrin carries Fe^{3+} in plasma and delivers iron from the sites of iron absorption (duodenal enterocytes and macrophages) to all tissues. Therefore, its level is higher in IDA. However, as it is an acute-phase protein, its level can be decreased during inflammation, despite normal or low iron stores.

Transferrin saturation (TSAT), an indicator of the iron load of circulating transferrin, gives an indirect measure of extent of iron utilization[16]. TSAT is the ratio of serum iron and total iron-binding capacity, multiplied by 100. It is decreased in both IDA and ACD. Pregnancy and oral contraceptives increase plasma transferrin levels; therefore, TSAT may be low in such patients, despite normal iron stores[16]. Hepcidin is increased during inflammation and decreased in IDA. It prevents iron absorption, causes retention of iron in the macrophages, and inhibits erythropoiesis.

Soluble transferrin receptor (sTfR) is a measure of erythropoietic activity. It is directly proportional to erythropoietic activity and inversely proportional to tissue iron availability[28]. sTfR is used to differentiate iron deficiency (increased sTfR and low serum ferritin) from inflammation (normal sTfR and serum ferritin) and to diagnose a combination of iron deficiency and inflammation (increased sTfR and normal serum ferritin)[24,27]. However, its use is limited due to its cost and unavailability in many laboratories.

The sTfR/log ferritin ratio (sTfR-ferritin index) may be an early indicator of depletion of iron stores[29]. A ratio < 1 suggests ACD and excludes iron deficiency, while a ratio > 2 suggests either IDA or mixed IDA and ACD[27].

Functional iron deficiency is the imbalance between the iron requirements of the erythroid marrow and the iron supply, when the body cannot supply iron rapidly enough to maintain an increased erythropoietic rate. This leads to reduced reticulocyte and erythrocyte cellular hemoglobin (Hb) content[30]. Reticulocyte hemoglobin content (CHr) and the percentage of hypochromic RBC are indicators of red cell hemoglobinization and, thus, functional iron deficiency, regardless of inflammatory states[30]. In IDA, CHr > 40 and hypochromic RBCs > 5%[31].

Iron binds to protoporphyrin IX to form heme. In the absence of iron, zinc binds to protoporphyrin to form zinc protoporphyrin (ZPP). ZPP indicates iron levels in the bone marrow during erythropoiesis and is unaffected by ACD or inflammation[16].

MANAGEMENT OF IRON DEFICIENCY ANEMIA IN IBD

Goals of therapy

It is important to realize that IDA commonly accompanies IBD. The treatment of IDA should not be overlooked. Iron supplementation should be started as soon as a patient is found to have iron deficiency anemia. If a patient has iron deficiency without anemia, the decision to initiate iron therapy depends on the clinical scenario and the patient's preference[24]. The treatment options *vs* frequent laboratory monitoring should be discussed with the patient. The decision to initiate therapy and the type of therapy is determined by symptoms, severity of anemia, IBD disease activity, comorbidities, and risks associated with therapy[24]. Anemia impairs quality of life, even in the absence of specific symptoms, in patients with IBD. Iron therapy leads to significant improvement in the quality of life (QOL)[32]. Therefore, the therapeutic goals of IDA are to normalize hemoglobin, serum ferritin, and TSAT levels, replenish iron stores (serum ferritin > 100 g/L), avoid the need for blood transfusions, and improve the QOL. Three treatment options are available for iron deficiency anemia in IBD: oral iron, parenteral iron, and erythropoietin[33].

Response to therapy

After starting iron therapy, an increase in reticulocyte count occurs within 2 wk, hemoglobin rises by 2 g/dL within 4 wk, and hemoglobin level returns to normal within 8 wk. Oral iron therapy should be continued for at least 6 mo after the hemoglobin has normalized, in order to replenish iron stores[34].

To assess the response to therapy, hemoglobin should be measured within 4 wk of the initiation of iron therapy. After 4 wk of iron therapy, response to treatment is considered appropriate or optimal, if hemoglobin rises by at least 2 g/dL; partial, if hemoglobin rises by 1-1.9 g/dL; absent, if hemoglobin rises less than 1 g/dL[24,35].

If the response to iron therapy is suboptimal, oral iron administration should be changed to intravenous iron therapy, erythropoietic agents should be added to intravenous iron therapy, or causes of anemia should be reassessed. A serum ferritin > 100 g/L indicates appropriate iron stores in a patient taking oral iron[24]. Serum ferritin is falsely high and is not useful for monitoring intravenous iron supplementation, in such cases a TfS > 50% indicates iron overload[36].

Oral iron therapy

Indications[16]**:** Anemia with hemoglobin > 10 g/dL, Quiescent or mildly active disease, in which oral iron absorption is not affected[37] in the absence of absolute indications for intravenous therapy (as mentioned below).

Advantages: There are some advantages, *e.g.*, convenience and inexpensive, in oral iron therapy.

Limitations[33]**:** (1) intolerance and non-compliance due to side effects: abdominal pain, nausea, bloating, diarrhea; (2) impaired absorption due to duodenal inflammation, intestinal resection, severe disease activity; (3) partial or incomplete absorption; (4) non-absorbed iron can be toxic and worsen disease activity in IBD as a result of oxidative stress, neutrophilic infiltration, increased cytokines, and activation of NF-

kappa B[38]; (5) experimental studies in animal models showed increased colon carcinogenesis with oral iron supplementation by inducing local oxidative stress at sites of active inflammation[39,40]; (6) slow response to therapy, cannot compensate for ongoing excessive blood loss; and (7) effective for short periods.

Available oral iron formulations: (1) ferrous fumarate has 106 mg elemental iron/tablet; (2) ferrous sulfate has 65 mg elemental iron/tablet; (3) ferrous gluconate has 28-36 mg iron/tablet; and (4) ferrous sulfate Elixir: 44 mg/5 mL (used if intolerant to oral iron tablets).

A maximum of 10-20 mg of oral iron can be absorbed per day. The recommended maximum daily dose is up to 100 mg elemental iron per day, as higher doses do not increase its absorption and efficacy, and the side effects of oral iron are dose-related[24,26]. Oral iron should be started at a low dose after meals. If well tolerated, the dose can then be increased and should be taken on an empty stomach to increase absorption. Iron should be given two hours before, or four hours after, ingestion of antacids. Iron is best absorbed as the ferrous (Fe^{++}) salt form in a mildly acidic medium, so a 250 mg ascorbic acid tablet or a half-glass of orange juice can be added at the time of iron administration to enhance the degree of iron absorption. Soy protein, dietary calcium, phytates (bran, oats, rye), cereals, tea, antacids such as H2 receptor blockers, and proton pump inhibitors prevent absorption of nonheme iron.

Intravenous iron therapy
According to the international consensus statement, the preferred route of iron supplementation in IBD is intravenous[24].

Indications[24,41]**:** (1) severe anemia, hemoglobin < 10 g/dL; (2) intolerance to oral iron therapy; (3) failure of oral iron therapy; (4) need for quicker and prolonged response; and (5) active disease (CRP > 5 mg/L).

Advantages[34]**:** (1) repletion of iron stores in unaffected by inflammation, intestinal resection; (2) rapid reversal of IDA; (3) relatively better tolerance and fewer side effects; (4) compliance can be monitored; (5) a single dose is sufficient for a few intravenous (IV) iron formulations (ferric carboxymaltose; low-molecular weight iron dextran); and (6) concurrent use of erythropoietin.

Limitations: (1) need for IV access and hospital staff for administration; (2) expensive; (3) inconvenience (travel, obtain IV access); and (4) iron dextran causes life-threatening anaphylactic reactions.

Available IV iron formulations: There are various IV iron preparations currently available for treatment of IDA. Their country-to-country availability, manufacturers, dosing, maximum and minimum infusion times, adverse reactions, costs, and FDA pregnancy category are provided in Table 3. The use of high molecular weight iron dextran is obsolete, due to the associated high risk of life-threatening anaphylactic reactions.

Low molecular weight (LMW)-iron dextran (Cosmofer, INFeD) is more efficacious than oral iron in significantly raising hemoglobin levels within 8 wk[42]. LMW-iron dextran was associated with IgE-mediated anaphylactic reactions in up to 5.7% of patients during test dose infusion in a case-matched study[42,43]. Therefore, a black box warning that a test dose is required prior to its infusion is now included in the package insert. Its administration is time-consuming and infusions can take up to 4-6 h.

Iron gluconate (Ferrlecit) is indicated for patients with chronic kidney disease (CKD) receiving hemodialysis and supplemental epoetin therapy. A test dose is not required prior to its use. It has benzyl alcohol as a preservative.

Iron sucrose (Venofer) is indicated for IDA in CKD patients and requires a test dose only in Europe. It has been widely used for IDA due to its efficacy, safety, and better tolerability[44]. But, its use has been limited, due to an increased number of applications, and its infusion can take up to 3.5 h.

Ferric carboxymaltose (Ferinject, Injectafer) has been studied in patients with iron deficiency of different etiologies, such as non-dialysis and dialysis-dependent chronic kidney disease (CKD), IBD, heavy menstrual bleeding, post-partum IDA, or patients with chronic heart failure and IDA. It has been shown to be efficacious and well-tolerated when compared with oral iron[45] and iron sucrose[46].

Ganzoni's formula is useful to estimate individual iron requirements[47]: Iron deficit (mg) = body weight (kg) x [target Hb-actual Hb (g/dL) x 2.4] + stored iron (500 mg).

However, it is inconvenient, inconsistently applied in clinical practice, and underestimates iron requirements[45]. A simplified method was used by the authors to calculate the cumulative iron dose (Table 4) for the ferric carboxymaltose group, instead of the traditional Ganzoni's formula used in the iron sucrose group[46]. Ferric carboxymaltose is administered in 1-2 infusions, with each infusion given one week apart. It can be infused in 15 min, thus increasing the compliance rate. The use of ferric carboxymaltose for IDA was shown to be more cost effective and convenient than iron sucrose[48]. Transient hypophosphatemia, without clinical symptoms, was observed in a clinical study[46].

Ferumoxytol (Rienso, Feraheme) is indicated for IDA in patients with chronic kidney disease (CKD). It has a rapid administration time (minimum of 17 s for 510 mg dose), with a second dose given in 3-8 d. However, the safety and efficacy of infusion of 1020 mg of ferumoxytol over 15 min has been demonstrated in a single arm, open-label trial conducted at one center[49].

Table 3 Available preparations for intravenous iron supplementation[16,24,26]

	Iron dextran (LMW)	Iron gluconate	Iron sucrose	Ferric carboxymaltose	Ferumoxytol	Iron isomaltoside
Product/Europe	CosmoFer®	Ferrlecit®	Venofer®	Ferinject®	Rienso®	Monofer®
Product/United States	INFeD®	Ferrlecit®	Venofer®	Injectafer®	Feraheme®	Not available in United States
Manufacturer	Pharmacosmos	Sanofi-Aventis	Vifor	Vifor	AMAG	Pharmacosmos
Test dose required	Yes	No	Yes (in Europe)/No	No	No	No
Maximum approved dose	20 mg/kg	125 mg	200 mg (500 mg in few countries) 7 mg/kg	Ferinject- 1000 mg, or up to maximum of 20 mg/kg Injectafer-1500 mg if patient's weight > 50 kg 15 mg/kg if < 50 kg	1020 mg	20 mg/kg
	Iron dextran (LMW)	Iron gluconate	Iron sucrose	Ferric carboxymaltose	Ferumoxytol	Iron isomaltoside
Maximum injectable single dose	100 mg (2 mL)	125 mg (10 mL)	200 mg (10 mL)	Ferinject- 1000 mg or up to maximum of 20 mg/kg Injectafer- 750 mg (15 mL)	510 mg (17 mL)	200 mg (2 mL)
Maximum infusion time	360 min (6 h)	30-60 min	210 min (3.5 h)	15 min	15 min	15 min
Maximum injection time	2 min	10 min	5-10 min	Bolus push over 7.5 min	17 s (1 mL/s)	Bolus push
Dose-related reactions	Dextran induced IgE -mediated anaphylaxis, hypotension, edema	Hypotension, edema	Hypotension, edema	None reported	None reported	None reported
Relative risk of adverse side effects	Moderate	Low	Very low	None reported	Very low	None reported
Costs per 500 mg in €[1]	84-86 €	52-56 €	105-100 €	170-175 €	82.12	170-175 €
Costs per maximum single injectable dose in United States dollars	$37.70	$76.32	$120	$993.75	$658.54	Not available
FDA Pregnancy category	INFeD-category C Cosmofer - no data available	B	B	C	C	Can be used in 2nd and 3rd trimester
Additional comments		FDA approved for IDA in CKD receiving hemodialysis and supplemental epoetin therapy	FDA approved for IDA in CKD patients	Has been studied in patients with IDA associated with CKD either dialysis and nondialysis dependant, IBD, CHF, post-partum and pregnancy patients. Transient hypophosphatemia has been reported	FDA approved for IDA in CKD patients May transiently interfere with "tissue" diagnostic ability of MRI for up to 3 mo and "vascular" MRI for up to 2 d	Very low immunogenic potential

[1]In Germany August 2012. Prescribing information of marketed products, package inserts. LMW: Low molecular weight; CKD: Chronic kidney disease; CHF: Congestive heart failure; IDA: Iron deficiency anemia; IBD: Inflammatory bowel disease.

Table 4 Determination of the Cumulative Iron Dose[46]

Hemoglobin (g/dL)	Body weight < 70 kg	Body weight > 70 kg
> 10	1000 mg	1500 mg
7-10	1500 mg	2000 mg

Ferumoxytol is composed of superparamagnetic iron oxide nanoparticles coated with a low molecular weight semisynthetic carbohydrate. This agent may transiently interfere with the tissue diagnostic ability of MRI for up to 3 mo, and with vascular MRI for up to 2 d, which is a limitation for patients with IBD who will need an MRI within 3 mo[50]. If MR imaging is required within 3 mo after ferumoxytol administration, T1- or proton density-weighted MR pulse sequences are used to minimize the effects of the agent, and the radiologist should also be notified.

Iron isomaltoside 1000 (Monofer) is the newest IV iron product, but it is not available in the United States. This agent has very low immunogenic potential and a very low content of labile and free iron, enabling
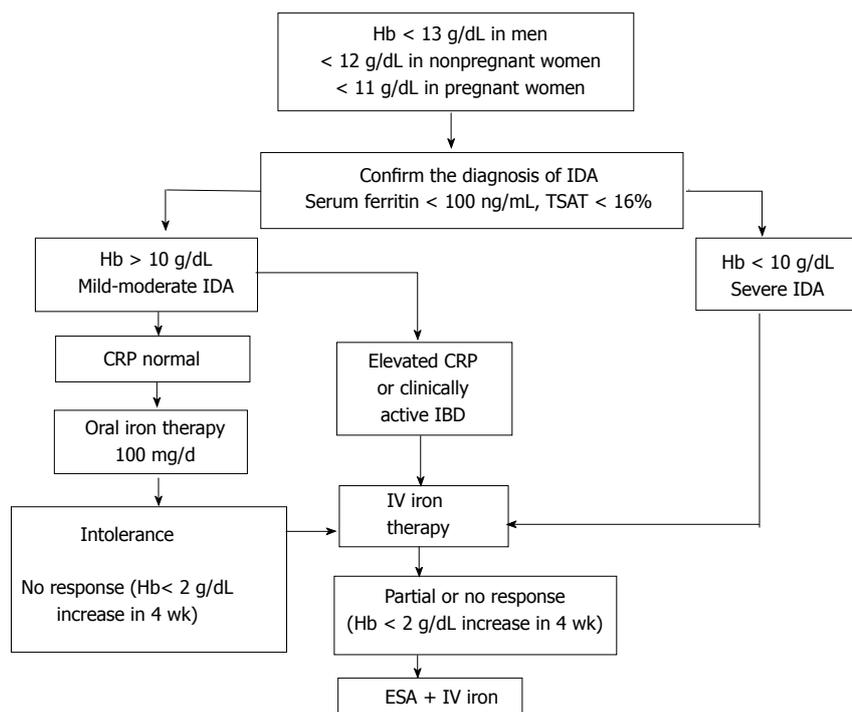
Figure 4 Management of iron deficiency anemia in patients with inflammatory bowel disease[16]. Hb: Hemoglobin; IDA: Iron deficiency anemia; TSAT: Transferrin saturation; CRP: C-reactive protein; IBD: Inflammatory bowel disease; IV: Intravenous; ESA: Erythropoiesis stimulating agents.

healthcare workers to administer a rapid high-dose infusion in doses exceeding 1000 mg in a single infusion, without the need for a test dose[51].

Erythropoiesis-stimulating agents

There is a component of anemia that is secondary to chronic inflammation in patients with IBD. Erythropoiesis-stimulating agents (ESA) are expensive and have risks associated with their administration. Therefore, these agents are recommended for treatment of anemia associated with IBD in patients who do not respond to IV iron therapy, when immunosuppressive therapy has not suppressed inflammation, and for patients requiring blood transfusions[52].

When patients are treated with ESAs, functional iron deficiency develops. Functional iron deficiency refers to the failure of iron supply or transport and insufficient availability of iron for erythropoiesis, despite normal body iron stores. Therefore, ESAs are used in combination with IV iron therapy[52]. The increased hepcidin levels in ACD prevent oral absorption of iron. Therefore, IV iron supplementation should be given instead of oral iron.

Blood transfusions

The need for red blood cell transfusion depends on the rate of bleeding, hemodynamic stability, hemoglobin level, and comorbidities. It is not a substitute for treatment of IDA with oral or IV iron supplementation. Its use in chronic anemia should be avoided, due to potential side effects and cost[24].

CONCLUSION

IDA is the most common anemia in IBD. Therefore, anemic patients with IBD should be evaluated for IDA. IDA mandates adequate and appropriate treatment, as it influences the patient's quality of life and morbidity. It should be considered as an extraintestinal manifestation of IBD. The basic workup may be insufficient to diagnose IDA in the presence of inflammation. Table 2 summarizes the laboratory parameters necessary to differentiate IDA from ACD. Recent clinical trials support IV iron therapy as a preferable option, especially in clinically active IBD and moderate-severe IDA. IV iron therapy was shown to have better tolerability and efficacy, with fewer infusions, a better safety profile, and, accordingly, improved patient compliance. Figure 4 summarizes the management of IDA in IBD[16]. The ultimate goal is to normalize hemoglobin levels.

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