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REVIEW

Anemia and iron deficiency in gastrointestinal and liver conditions

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Abstract

Iron deficiency anemia (IDA) is associated with a number of pathological gastrointestinal conditions other than inflammatory bowel disease, and also with liver disorders. Different factors such as chronic bleeding, malabsorption and inflammation may contribute to IDA. Although patients with symptoms of anemia are frequently referred to gastroenterologists, the approach to diagnosis and selection of treatment as well as follow-up measures is not standardized and suboptimal. Iron deficiency, even without anemia, can substantially impact physical and cognitive function and reduce quality of life. Therefore, regular iron status assessment and awareness of the clinical consequences of impaired iron status are critical. While the range of options for treatment of IDA is increasing due to the availability of effective and well-tolerated parenteral iron preparations, a comprehensive overview of IDA and its therapy in patients with gastrointestinal conditions is currently lacking. Furthermore, definitions and assessment of iron status lack harmonization and there is a paucity of expert guidelines on this topic. This review summarizes current thinking concerning IDA as a common co-morbidity in specific gastrointestinal and liver disorders, and thus encourages a more unified treatment approach to anemia and iron deficiency, while offering gastroenterologists guidance on treatment options for IDA in everyday clinical practice.

Key words: Iron deficiency anemia; Gastrointestinal bleeding; Nonsteroidal anti-inflammatory drugs; Gastritis; Infection; Bariatric surgery; Celiac disease; Gastrointestinal neoplasm; Chronic hepatitis; Non-alcoholic fatty liver disease

Core tip: Iron deficiency anemia (IDA) frequently originates in the gastrointestinal (GI) tract and is a common cause of patient referral to gastroenterologists. Guidelines for the management of IDA in GI conditions are lacking. Symptoms such as fatigue and impaired exercise capacity should prompt a diagnostic work-up for anemia (hemoglobin), iron status (transferrin saturation, ferritin) and inflammation (C-reactive protein). Treatment of IDA should aim to restore normal hemoglobin levels, red cell indices and iron status. Intravenous administration is the preferred iron treatment in patients with chronic GI bleeding, patients being unresponsive or intolerant to oral iron and patients requiring rapid hemoglobin correction.

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INTRODUCTION

Iron deficiency anemia (IDA) is a common complication in routine clinical practice that frequently originates in the gastrointestinal (GI) tract[1-3]. Patients with IDA are therefore often referred to gastroenterologists for further examination and/or treatment. IDA associated with GI disorders can substantially reduce quality of life, contribute to fatigue, and may even lead to hospitalization[4,5].

In contrast to the well-documented inflammatory bowel disease (IBD)-associated IDA[6,7], prevalence data for IDA associated with other pathological conditions of the GI tract are sparse (Table 1). Guidelines for the diagnosis and management of anemia and iron deficiency are available for IBD[8], but not for other GI conditions. Overall, there are three main pathological contributors to IDA, namely chronic bleeding, malabsorption and inflammation[9-13]. However, other factors, such as poor or selective diet, as well as iron malabsorption (*e.g.,* due to decreased gastric pH) should not be neglected in patients referred for IDA assessment. This applies particularly to elderly patients[14-18].

Despite the increasing availability of effective and well-tolerated parenteral iron preparations for the treatment of IDA[19,20], a comprehensive overview of treatment approaches of IDA in GI conditions is currently lacking. Furthermore, definitions of IDA are inconsistent across clinical studies and publications, with the terms "iron deficiency", "iron deficiency anemia" and "anemia" being used almost interchangeably. In addition, the diagnostic markers and cut-off levels used to define iron deficiency vary widely. While anemia is clearly defined according to the World Health Organization as a hemoglobin (Hb) level < 12 g/dL in women (< 11 g/dL in pregnant women) and < 13 g/dL in men, the situation is ambiguous for iron deficiency. Commonly, serum ferritin levels below 15-100 ng/mL (depending on the presence of concomitant inflammation) and transferrin saturation (TSAT) below 16%-20% are considered indicative of iron deficiency[1,7,8].

These aspects complicate the interpretation and comparability of data and highlight the need for standardization of definitions and proper assessment of iron status across different GI and liver diseases. Recently published reviews on IDA discuss IDA in general[21,22] but give only little attention to the fragmented yet consistent evidence that IDA is a common issue in most GI conditions. The aim of this review is therefore to illustrate how IDA represents a common co-morbidity in these disorders, and to encourage a more unified treatment approach to GI condition-associated anemia and iron deficiency (ID).

Relevant articles were identified by screening the PubMed database for articles on IDA or ID in the context of GI or liver disease and associated illnesses. Data reported in abstract form only were identified by manual search through abstracts from major congresses in the field. In addition, the authors' own literature databases were screened for suitable publications. The results were filtered for articles with information on anemia prevalence and/or anemia management. The last search was conducted in June 2015.

ANEMIA AND ID IN DIFFERENT CONDITIONS

Esophagitis and hiatal hernia

Gastric bleeding from Cameron lesions in large diaphragmatic or hiatal hernia is an established cause of IDA[23,24]. However, axial and paraesophageal hernia without Cameron lesions can also be associated with IDA[25]. The reported incidence of IDA for all types of hernia ranges from 8% to 42%, with an average of 20%[26].

Hiatal hernia increases the risk of IDA independent of comorbid esophagitis[27]. Suggested causes of hernia-related IDA are mechanical trauma plus esophagitis, erosions or gastro-esophageal acid reflux[25,26].

Notably, the absence of endoscopic evidence of erosions in the majority of patients with hernia-related IDA does not exclude their causal role[26]. Therefore,

Table 1 Overview of diseases considered to be associated with iron deficiency/iron deficiency anemia

Conditions	Anemia or IDA prevalence	Predominant pathological contributors to anemia			Association with anemia and ID
		Bleeding	Malabsorption	Inflammation	
Nonvariceal upper GI bleeding[33]	80%	√			> 80% of patients admitted to hospital with nonvariceal AUGIB were anemic at the time of discharge
Celiac disease[87-89]	32%-69%		√	√	Well-established relationship between celiac disease and IDA Most widely cited cause of IDA is abnormal iron absorption, but bleeding and inflammation are also known contributory factors
Intestinal parasitic infections[151]	33%-61%	√	√		*T. trichiura* and hookworm infections are closely associated with IDA
GI cancers[107,108,111,117,121-120]	50%-60%	√		√	CRC: IDA associated with greater tumor diameter and with cancers of the right side of the colon Polyps: IDA much more common with malignant polyps than benign polyps GIST: Most frequent presentation is GI bleeding, which can result in anemia. In pediatric GIST, anemia is the most frequent clinical finding Gastric cancers: 6.8-fold relative risk of gastric cancer in patients with Pernicious anemia Small bowel malignancies: Anemia among most common presenting symptoms Esophageal cancers: Patients with Fanconi anemia at increased risk
Esophagitis and hiatal hernia[23-26]	8%-42%	√			Gastric bleeding from hernia is an established cause of IDA Even in absence of visible lesions, large hernia may be a possible cause of IDA with unexplained etiology
Bariatric surgery[77,196]	10%-40%		√		ID and anemia are well-known risks after bariatric procedures, but causes are multifactorial and vary depending on exact procedure and patient population
Intestinal failure[101-103]	30%-37%	√	√		Intestinal failure is associated with ID due to malabsorption, GI blood loss, and multiple surgery
Diverticular disease[144]	25%	√			One of the most common causes of lower GI bleeding leading to IDA Increasing prevalence due to rise in elderly population
Restorative proctocolectomy[153]	6%-21%	√	√		IDA due to mucosal bleeding and impaired iron absorption in patients developing symptomatic or asymptomatic pouchitis
NSAID-associated fecal blood loss[1]	10%-15%	√			Even low dose aspirin and non-aspirin-NSAIDs increase mean fecal blood loss 2-4-fold compared with normal
Angiodysplasia[1]	5%	√			Most common cause of lower GI bleeding in the elderly
Gastric antral vascular ectasia (GAVE)[1,48,55]	1%-2%	√			Chronic, slow bleeding is typically associated with IDA
Gastritis[57,66]	NA		√	√	*H. pylori* infection suggested to play important role in development of IDA
Peptic ulcer[197]	NA		√	√	H. pylori infection and IDA as above. Additionally, bleeding from ulcer
Chronic hepatitis and liver conditions with GI bleeding[155]	75%	√			Chronic liver disease can be complicated by anemia, particularly due to bleeding
Non-alcoholic fatty liver disease (NAFLD)[171]	NA			√	One-third of adult NAFLD subjects are reported to be iron deficient, defined by a TSAT < 20%

H. pylori: *Helicobacter pylori*; AUGIB: Acute upper gastrointestinal bleeding; CRC: Colorectal cancer; GI: Gastrointestinal; GIST: Gastrointestinal stromal tumors; ID: Iron deficiency; IDA: Iron deficiency anemia; NA: Not available.

even if no lesions are visible during endoscopy, larger hiatal hernia should still be considered as a possible cause of IDA with unexplained etiology.

Surgery in combination with proton pump inhibitor (PPI) therapy is evidently no better than PPI therapy alone in treating and preventing the recurrence of IDA, even in the case of larger hiatal hernia[26].

Nonvariceal upper GI bleeding

Acute upper gastrointestinal bleeding (AUGIB) is a common disorder associated with a high mortality rate of 3% to 15%[28-30]. While peri-endoscopic management of AUGIB, including blood transfusions, has been well characterized and standardized[31,32], guidelines for the monitoring and treatment of IDA in

patients after non-variceal AUGIB are still lacking.

Recently, a retrospective study showed that more than 80% of patients admitted to hospital with non-variceal AUGIB were anemic at the time of discharge[33]. Of these, only 16% received a recommendation to begin oral iron supplementation while intravenous iron was not even considered, demonstrating that post-discharge anemia is often disregarded.

Studies analyzing the clinical impact and risks associated with anemia after AUGIB are scarce. One study revealed that patients with hemoglobin (Hb) values < 10 g/dL after AUGIB had two-fold greater risks of re-bleeding and mortality than patients with Hb values ⩾ 10 g/dL[34].

A double-blind, placebo-controlled trial, recently demonstrated that patients with IDA after non-variceal AUGIB clearly benefit from iron supplementation[9]. In this study, oral and intravenous iron appeared to be equally effective in raising Hb levels, probably since most patients were not iron deficient at enrolment. However, iron stores (measured as serum ferritin) were replenished most effectively with intravenous iron supplementation.

Regarding the transfusion of red blood cell concentrates (RBC), a recent study in patients with AUGIB (TRIGGER)[35] suggests that the Hb threshold for RBC transfusion can be safely lowered without adversely affecting clinical outcomes. This is in line with results in other indications such as cardiac surgery, critical care and hip surgery. Accordingly, restrictive Hb thresholds (< 8.0 g/dL) should be considered except for patients with ischemic heart disease as pre-existing comorbidity[35,36].

NSAID-associated fecal blood loss

The administration of nonsteroidal anti-inflammatory drugs (NSAIDs) is known for its association with upper and lower GI injury[37-39]. This injury can include bleeding[40-42] which may be severe enough to result in hospitalization[43,44]. Even low dose aspirin as well as non-aspirin-NSAIDs increase mean fecal blood loss from roughly 0.5 mL/d to 1-2 mL/d (*i.e.,* 0.5-1.0 mg iron loss/d)[42]. Among patients treated with aspirin doses ⩾ 1800 mg/d, 31% had a blood loss of ⩾ 5 mL/d (*i.e.,* ⩾ 2.5 mg iron loss/d). Although cyclooxygenase-2 (COX-2) inhibitors are associated with fewer GI injuries than traditional NSAIDs, long-term use of a COX-2 inhibitor may also induce GI injuries and require concomitant medication for associated anemia and small intestinal injuries[45]. Notably, routine endoscopic examination may not reveal NSAID-induced GI injuries. Therefore, capsule endoscopy is recommended to screen for GI injuries in patients taking NSAIDs and presenting with unexplained anemia or ID[41,45,46].

Portal hypertensive gastropathy and gastric antral vascular ectasia

Portal hypertensive gastropathy (PHG) and gastric antral vascular ectasia (GAVE), although being distinct entities[47], can cause chronic gastrointestinal blood loss in patients with liver cirrhosis[48,49]. Most frequently found in association with liver cirrhosis, PHG can also occur in non-cirrhotic patients (*e.g.,* splanchnic venous thrombosis)[50]. The management of PHG is based on reducing hepatic venous pressure gradients and iron replacement therapy and/or blood transfusions. Severe cases may require shunt procedures[51-53].

GAVE, first described in 1953[54] in a patient with chronic IDA, accounts for up to 4% of all non-variceal upper gastrointestinal bleedings. Although cirrhosis is found in up to 30% of GAVE patients and occurs in about 2% of patients awaiting liver transplantation[49,55,56], portal hypertension does not seem to play an important role in the development of GAVE. Treatment comprises, in general, endoscopic interventions (*e.g.,* Argon plasma coagulation, Nd: YAG laser) and surgical procedures (*e.g.,* antrectomy and Billroth I anastomosis) to manage lesions, and symptomatic therapy with iron supplementation or blood transfusions, depending on the severity of anemia[49-52].

Autoimmune atrophic gastritis

Autoimmune gastritis (AIG) is implicated in 20%-30% of IDA cases that are refractory to oral iron[57,58].

AIG, first described by Faber in 1909 as *achlorhydric gastric atrophy*, is a chronic progressive inflammatory condition leading to the decrease or disappearance of parietal cells, which results in reduced or absent acid production (hypochlorhydria or achlorhydria)[59].The lack of gastric acidity has only recently been confirmed as key factor for impaired intestinal iron absorption[60]. IDA is more often associated with AIG than classical pernicious anemia and frequently precedes vitamin B_{12} deficiency (at least in fertile women)[61,62].

Helicobacter pylori gastritis

IDA is a recognized extragastric manifestation of *Helicobacter pylori* (*H. pylori*) infection[63]. Over 50% of patients with unexplained refractory IDA have active *H. pylori* infection[57,58]. Data, showing that *H. pylori* eradication reverses IDA, were confirmed by several observational and interventional trials, subsequently summarized in two meta-analyses of randomized controlled trials[57,64,65]. Accordingly, the Maastricht IV *H. pylori* consensus report[66] and other national and international guidelines[67-69] recommend *H. pylori* eradication for the treatment of IDA of unknown origin. Notably, Bismuth-based eradication therapy is more effective in terms of increasing hemoglobin and iron stores than first line PPI-based triple therapy in patients with IDA and *H. pylori* infection[63].

Discussed mechanisms underlying the pathogenesis of *H. pylori*-related IDA include occult chronic GI bleeding due to gastric mucosal microerosions, competition for dietary iron by the bacteria, reduced

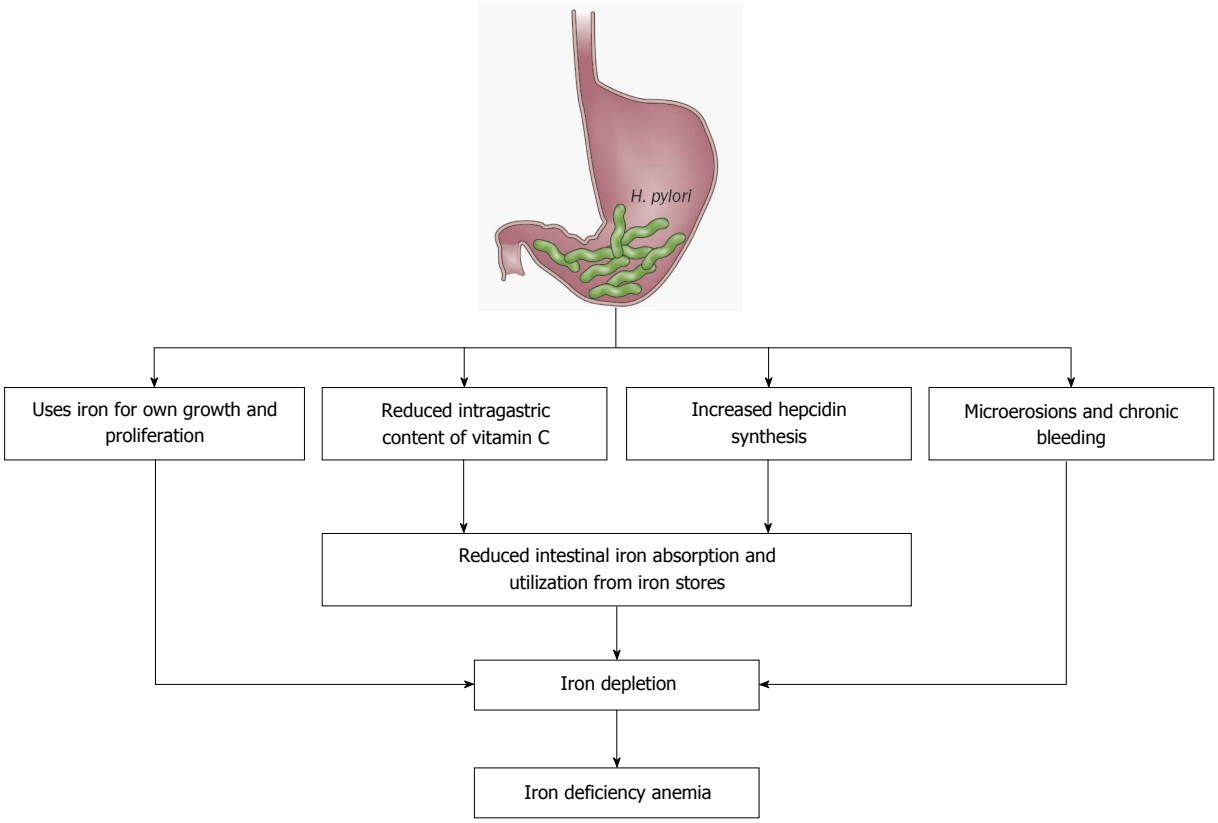

Figure 1 Pathogenic mechanisms proposed to be involved in the association of iron deficiency anemia and *Helicobacter pylori* infection[63].

ascorbic acid concentration in the gastric juice, affecting the absorption of dietary iron and upregulation of proinflammatory cytokines and hepcidin, the key regulator of iron homeostasis (Figure 1)[57,70-72]. In one study, *H. pylori* strains retrieved from patients with IDA exhibited faster, iron-dependent cell growth and an enhanced iron uptake than strains from patients without IDA[73]. Furthermore, *H. pylori* accelerates the development of inflammation, dysplasia and adenocarcinoma (mediated by the H. pylori virulence factor cytotoxin-associated gene A [CagA]) in an ID environment[74-76]. CagA also facilitates *H. pylori* colonization through iron acquisition, indicating that CagA provides a survival advantage for *H. pylori* in this setting.

Bariatric surgery

There is growing evidence of potentially severe, occasionally even life-threatening, nutritional and pharmacological consequences of bariatric surgery[77]. ID and IDA after bariatric procedures can result from intestinal bleeding (*e.g.*, from marginal ulcers) or reduced iron absorption due to postoperative intolerance for red meat, diminished gastric acid secretion or exclusion of the duodenum from the alimentary canal[78,79].

The reported incidence of ID in patients following gastric bypass surgery ranges from 12% to 47%[77]. However, the interpretation of reported incidence rates is complicated by different definitions of ID and IDA, postsurgical follow-up periods, types of interventions and patient populations[80]. In a large, patient record review of 959 patients who underwent laparoscopic Roux-en-Y gastric bypass (RYGB) between 2001 and 2011, 51.3% were iron deficient and 6.7% required intravenous iron therapy[81]. Amongst these patients, the prevalence of ID is significantly higher in premenopausal women than in postmenopausal women and males (72% *vs* 35% and 20%). Comparing different types of surgery, a cross-sectional pilot study of 95 patients showed no significant difference in ID rates after RYGB or sleeve gastrectomy (30% *vs* 36.4%)[82].

Since oral iron substitution has been shown to be relatively ineffective following bariatric surgery, and tolerance to oral iron preparations is often poor, intravenous iron treatment has been put forward as a preferable option[77]. Some authors suggest that repeated doses of intravenous iron may be required over the course of a year[83].

Ferric carboxymaltose (FCM) showed promise for the treatment of IDA in five phase 3 clinical trials involving 281 patients who had undergone bariatric surgery[84]. FCM exhibited similar or improved efficacy in terms of increasing hemoglobin, ferritin and transferrin saturation (TSAT) values and a favorable safety profile compared with standard medical care (iron sucrose, ferric gluconate, iron dextran or oral

iron). In addition, FCM offered the possibility for larger single-dose administrations at fewer visits compared to iron sucrose, ferric gluconate and oral iron[84].

Celiac disease

Celiac disease is one of the most common chronic inflammatory conditions of the GI system, affecting about 1% of the population[85]. There is a well-established relationship between celiac disease and IDA[86]. Anemia is the most common presenting symptom of celiac disease, found in 32%-69% of adult patients[87-89]. Approximately 80% of anemic patients with celiac disease are also iron-deficient[88,89]. In 49% of anemic patients with celiac disease, ID was found to be the only detectable abnormality[87]. Conversely, among patients presenting with unexplained IDA, 5% have histologically-confirmed celiac disease[57,90,91].

Impaired iron absorption (due to villous atrophy of the intestinal mucosa) and blood loss are important pathological contributors to anemia in celiac disease[92]. Occult GI bleeding was detected in about half of patients with celiac disease adhering to a gluten-free diet[93]. In some patients, nutritional deficiencies may also be a (contributing) causative factor[94]. Inflammation is a major contributor to IDA, with interleukin (IL)-1, IL-6, IL-10, interferon (IFN)-γ and tumor necrosis factor (TNF)-α as inducers of hepcidin, the main regulator of iron homeostasis[92,95]. Accordingly, celiac disease-related IDA is refractory to oral iron treatment[57,92,96], and even after switching to a gluten-free diet, it takes 6-12 mo until most patients recover from anemia[97]. Notably, half of patients remain iron-deficient even after 1-2 years on a gluten-free diet. The slow or lacking recovery from ID may be due to the low absorption rate of nutritional iron (1-2 mg/d), which hinders the repletion of severely depleted iron stores, and the potentially low content of iron and other micronutrients in a gluten-free diet[98].

Therefore, patients with celiac disease clearly benefit from immediate intravenous iron treatment instead of switching to intravenous iron only after (foreseeable) non-response and/or intolerance to oral iron[96].

Intestinal failure

Intestinal failure (IF) results from obstruction, dysmotility, surgical resection, congenital defect, or disease-associated loss of absorption, and is characterized by the inability to maintain protein-energy, fluid, electrolyte, or micronutrient balance[99]. In patients suffering from IF, total parenteral nutrition (TPN) is a life-saving intervention until full or partial recovery of enteral nutrition (EN)[100]. Nevertheless, patients with IF are prone to ID as a result of malabsorption, gastrointestinal blood loss and multiple surgical procedures. Accordingly, ID is the most common micronutrient deficiency during and after transition from TPN to EN, with reported incidences of 60%-80% for ID, and 30%-37% for IDA[101-103]. A study from the Mayo Clinic, including 185 patients, showed that IDA developed much more rapidly in patients with fistula and bowel obstruction than in those with short bowel syndrome (SBS) and dysmotility[104]. Despite the high prevalence of ID, iron is not routinely added to parenteral nutrition formulations because of the risk of anaphylaxis and concerns about incompatibilities. Although data describing the compatibility of iron supplementation with parenteral formulations are conflicting[105], iron dextran has been found to be compatible with lipid-free solutions at an amino acid concentration > 2%[106]. A safer approach would prescribe intermittent infusion of therapeutic iron doses.

GI cancers

Anemia and IDA are common in patients with colorectal cancer (CRC), with a prevalence of 50%-60%[107-111]. Risk factors for anemia in patients with CRC are greater tumor diameter and cancer in the right side of the colon[108,112]. CRC is a cause of lower GI bleeding in 11% to 14% of cases[113], and malignant polyps are associated with greater blood loss and more frequent occurrence of IDA than benign polyps[114].

Anemia has also been described in the context of gastrointestinal stromal tumors (GIST), which are frequently associated with acute or chronic bleeding[115,116]. In pediatric GIST, anemia is the most frequent clinical finding (86% with symptomatic anemia)[117]. Notably, anemia is also one of the most frequent side effects of imatinib, the standard treatment for advanced/metastatic GIST, including small bowel cancers[118,119]. In addition to IDA, other specific forms of anemia such as pernicious anemia and Fanconi anemia are also increased in patients with gastric cancers (6.8-fold relative risk of pernicious anemia)[120], small bowel malignancies[121] and esophageal cancers[122].

Notably, ID (with or without anemia) is associated with an increased risk of GI malignancy 2 years after diagnosis of ID[123]. Therefore, unexplained IDA is an important measure for detection of GI malignancy[108]. In patients with advanced CRC, Hb levels < 11 g/dL are a poor prognostic factor[124] and prompt referral as well as investigation of IDA are recommended in patients with CRC[124-126] and cancers in general[127]. However, treatment options for IDA are not discussed, as the guidelines primarily focus on surgical follow-up for CRC.

Since CRC surgery may result in significant blood loss, perioperative allogeneic blood transfusion (ABT) has often been used in CRC patients[128,129]. However, ABT is associated with certain risks, such as an increased infective complication rate and increased disease recurrence[130-132]. Furthermore, ABT involves significant cost[133], and RBCs are an increasingly limited resource. Therefore, alternative options such as perioperative intravenous iron administration have been examined[19,128,129,134] and a multicenter

randomized controlled trial comparing intravenous ferric carboxymaltose with oral iron as preoperative anemia treatment in colorectal cancer patients is ongoing[135]. One randomized prospective placebo-controlled pilot study showed preoperative intravenous iron sucrose (total iron dose 600 mg) to have no effect on serum Hb concentration or the rate of blood transfusion in 62 patients scheduled for resection of suspected colorectal cancer[128]. However, the trial included only 11 patients with confirmed anemia, while 22 had a normal Hb, and in 29 patients, there was no recent record of anemia status at all. Furthermore, a Hb increase of 0.5 g/dL, defined as the primary endpoint, is clinically insignificant and unlikely to have an impact on perioperative transfusion requirements[136]. In general, a Spanish expert panel on alternatives to allogeneic blood transfusion suggests perioperative intravenous iron administration to anemic patients scheduled for gastrointestinal surgery[137]; yet overall, there are only few high-quality prospective studies of sufficient power[138].

Diverticular disease

Diverticular disease, one of the most common causes of lower GI bleeding[113,139], accounts for 30%-50% of massive lower GI bleeding cases[140]. Diverticulitis is a major healthcare problem which often requires surgical management to optimize patient outcomes[141]. Despite reports of IDA associated with clinical cases of diverticulitis[142,143], information on prevalence is lacking. In a study of 1124 cases of colonic diverticular disease seen at a hospital clinic during a 15-year period, 44 (3.9%) had diverticular hemorrhage and 25% of these patients had anemia (Hb < 12 g/dL)[144]. Anemia was most frequent in elderly patients (60 years and upwards) and those with acute bleeding.

Angiodysplasia

Angiodysplasia is a poorly understood clinical condition involving fragile, thin-walled vascular malformations which are susceptible to rupture, and may thus cause severe GI bleeding[145]. Angiodysplasia accounts for up to 5% of cases of GI bleeding overall and up to 40% of obscure GI bleeding cases[146,147]. Angiodysplasia has been found to be present in 61% of patients over the age of 60, often with co-existing conditions[148]. Chronic angiodysplasia can be difficult to manage due to frequent rebleeding of multiple lesions clustered in different localizations of the GI tract and therefore frequently results in chronic IDA[149].

In the past, patients with angiodysplasia commonly had numerous and frequent blood transfusions and suffered end-organ damage due to refractory anemia[149]. Modern intravenous iron preparations can be considered a valuable treatment option if blood loss exceeds 10 mL/d (*i.e.*, around 5 mg iron)[149].

Intestinal parasitic infections

Several studies have shown parasitic infections, especially *T. trichiura* and hookworm infections, to be closely associated with IDA[150-152]. Hookworm infections are associated with mucosal damage and endogenous loss of iron[151], while *T. trichiura* and *E. histolytica* cause bleeding and dysentery by invading the mucosa of the large intestine. Accordingly, intestinal parasitic infections are recognized as predictors of IDA.

Restorative proctocolectomy

A frequent complication of restorative proctocolectomy is pouchitis, which in turn is associated with IDA (6%-21% of patients with functional pouches) due to mucosal bleeding and impaired iron absorption[153]. Notably, pouchitis can be asymptomatic but still be associated with IDA, as can pouches in the abscence of pouchitis. In patients that are intolerant or unresponsive to oral iron, intravenous iron and erythropoiesis-stimulating agent (ESA) treatment can correct the anemia. Another deficiency, vitamin B_{12} deficiency, occurs in 25%-53% of pouch recipients (compared to 3%-40% in the general population), being also a frequent cause of anemia. In general, vitamin B_{12} deficiency can be resolved with oral cyanocobalamin[153,154], suggesting a post-procedural change in dietary habit as the main reason for this deficiency.

Chronic hepatitis and liver conditions

Among patients with chronic liver disease, 75% are anemic[155], mainly due to acute or chronic GI hemorrhage which may lead to iron deficiency as a consequence. Acute gastrointestinal hemorrhage is a potentially serious complication of portal hypertension and the second most common cause of mortality in patients with cirrhosis. The increased risk of bleeding in severe hepatocellular disease can result from impaired blood coagulation due to reduced synthesis of blood coagulation factors by hepatocytes, and lower thrombocyte numbers. Initial treatment aims to correct hypovolemia and restore stable hemodynamic function (*e.g.,* gelatin-based colloids, solutions of human albumin or red blood cell transfusion)[155]. In addition, IDA caused by chronic blood loss may be treated with oral iron or intravenous iron in cases of advanced chronic liver disease.

Notably, anemia is frequently associated with both peginterferon (PEG-IFN) and ribavarin (RBV) in the treatment of chronic hepatitis C virus (HCV) infection, particularly when these drugs are administered in combination[156-158]. According to the WHO guidelines, grade 1 anemia (Hb 10-11 g/dL) has been reported in up to 30% and grade 2 (< 10 g/dL) in 9%-10% of cases. The addition of direct-acting anti-virals (DAAs) such as telaprevir (TVR) or boceprevir (BOC) as part of

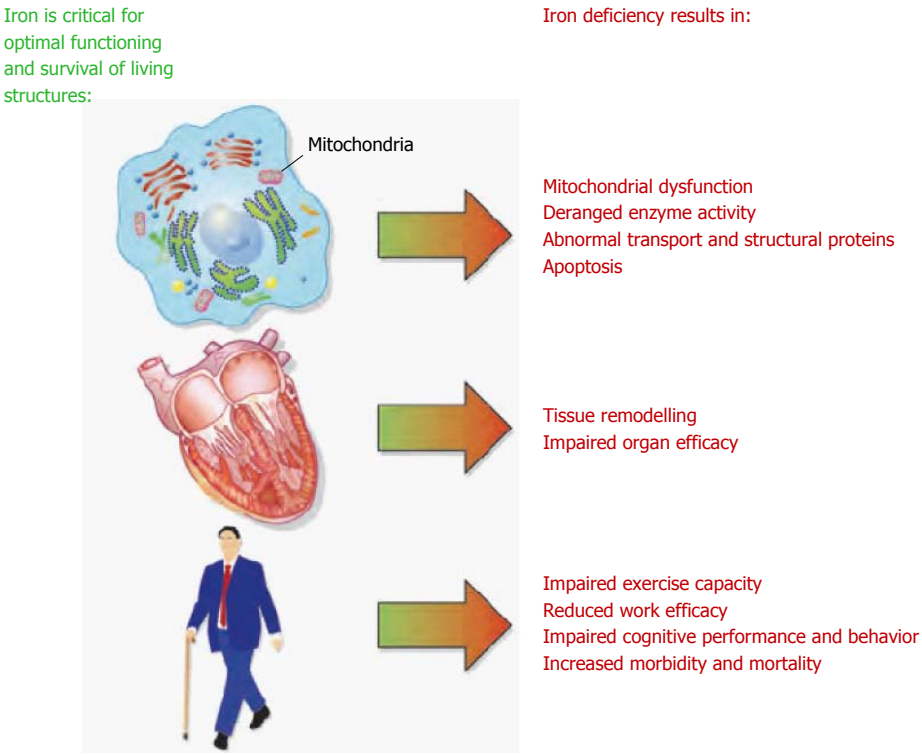

Figure 2 Role of iron in essential cellular functions[178].

the more effective antiviral triple combination therapy has been shown to increase anemia by up to 20% compared to PEG-IFN/RBV in both treatment-naïve and -non-naïve patients[159-163]. Since this treatment-induced anemia is mainly due to hemolysis, dose reduction of RBV by up to 50% is recommended, followed by administration of recombinant erythropoietin[156,164-166]. Evaluation of inosine triphosphatase polymorphisms may help to predict the risk of anemia and response to treatment[156,167-169]. Second generation DAAs, including simeprevir (SMV), sofosbuvir (SOF), daclatasvir (DCV), and ledipasvir (LDV), approved in combination (*e.g.*, SOF/SMV) as IFN-free regimens for the treatment of genotype 1 HCV infection, offer significantly greater cure rates and shorter treatment duration, and have been associated with lower incidence rates of anemia, ranging from 5% to 20%[170].

Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is becoming the most common liver disease worldwide (estimated prevalence of 25%-30%), with one-third of adult patients being iron deficient (TSAT < 20%)[171]. ID was significantly associated with female gender, obesity, increased BMI, lower alcohol consumption, non-white race and increased levels of IL-6 and IL-1ß. In contrast to patients with obesity-related, low-grade inflammation, serum hepcidin levels were low in NAFLD subjects with ID, reflecting an appropriate response of hepcidin signaling to ID. The authors concluded that initially, obesity-induced systemic inflammation may increase hepcidin levels and contribute to ID, but hepcidin is appropriately downregulated after ID is established[171]. Similar results of decreased intestinal iron absorption that are inversely associated with serum and urinary hepcidin levels have been reported in dysmetabolic iron overload syndrome (DIOS)[172] which is associated with half of NAFLD cases. Based on hepatic gene expression studies in pediatric patients with non-alcoholic steatohepatitis (NASH), it is hypothesized that, (1) a decreased level of transferrin receptor Ⅰ in NASH patients is an indicator of reduced erythropoietic activity in the bone marrow, a typical feature of anemia of chronic inflammation; and (2) that elevated expression of transferrin and transferrin receptor Ⅱ may result in the upregulation of hepcidin, leading to impaired duodenal iron absorption. In addition, the authors demonstrated that elevated serum ferritin levels do not reflect increased hepatic iron stores in patients with NASH, but are rather a consequence of hepatic and/or obesity-related inflammation[173].

DISCUSSION

While the origin of IDA is often multifactorial, a close relationship with various GI conditions has been established (Table 1)[1,2]. Nevertheless, management of patients with IDA often remains inadequate[1,4].

Even without anemia, ID can have a substantial impact on physical and cognitive function and quality of life (*e.g.*, fatigue)[174-177] (Figure 2). This supports

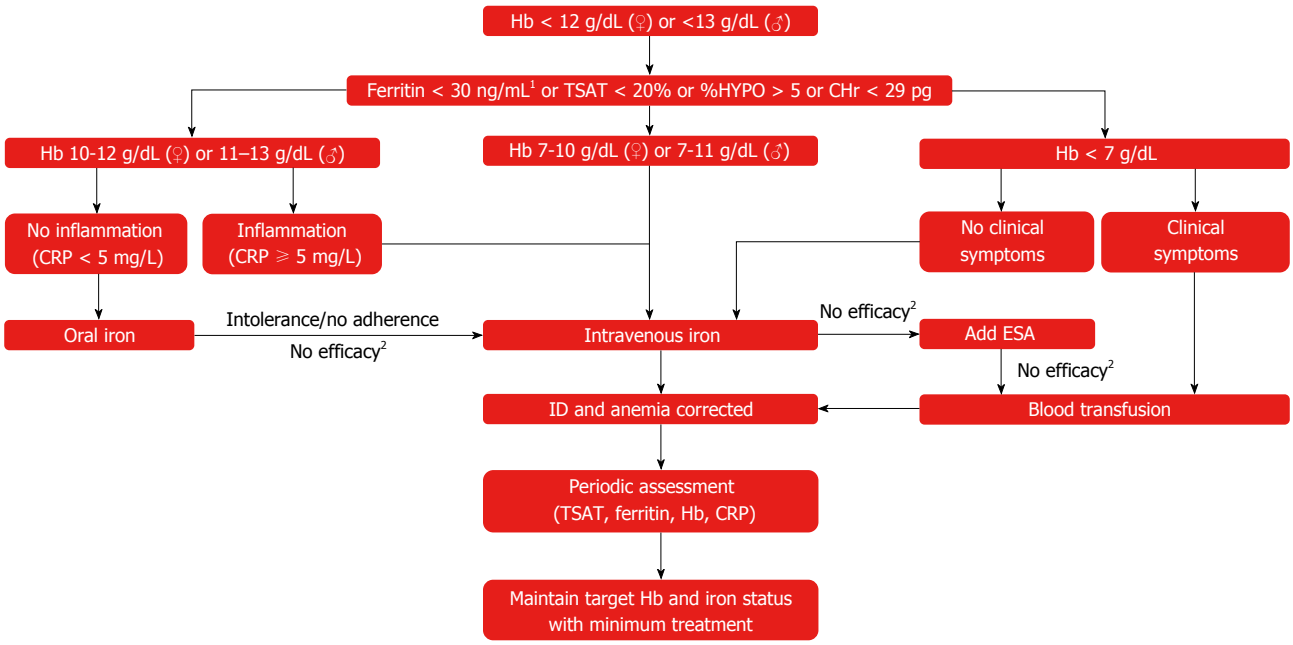

Figure 3 Suggested approach for the assessment and treatment of iron deficiency/iron deficiency anemia in clinical practice. [1]In patients with inflammation, ferritin levels < 100 ng/mL should be considered as iron-deficient; [2]Hb increase < 2 g/dL in 4 wk. Stein *et al*[6]. CHr: Hemoglobin content of reticulocytes; CRP: C-reactive protein; ESA: Erythropoiesis-stimulating agent; Hb: Hemoglobin; %HYPO: Percent hypochromic red blood cells; ID: Iron deficiency; IDA: Iron deficiency anemia; TSAT: Transferrin saturation.

the need for regular assessment of iron status and consideration of the clinical consequences of any disturbance of iron status. Patients with typical GI symptoms, such as epigastric pain, change in bowel habit, weight loss, early satiety, or poor appetite, should be assessed for ID and anemia, since these symptoms are often associated with acute or chronic blood loss, malabsorption and/or chronic inflammation[5]. In the planning of treatment for ID/IDA and the selection of the iron administration route, the frequency and magnitude of blood loss as well as the known side effects of oral iron should be considered[4].

Although chronic GI bleeding and malabsorption in GI conditions are well-recognized causes of ID/IDA[5,12,13], other factors such as age and chronic inflammation that inhibit iron availability via increased hepcidin levels should also be borne in mind[2,15,179]. Normal iron homeostasis is based on two pillars: absorption of nutritional iron by enterocytes in the duodenum and upper jejunum (1-2 mg/d), and recycling of iron *via* phagocytosis of senescent red blood cells (20-25 mg/d)[179]. Absorbed or recycled iron is transiently stored in the monocytes/macrophages of the reticuloendothelial system, from where it is released *via* ferroportin, loaded on transferrin and transported to the bone marrow for erythropoiesis. Hepcidin is a key regulator of iron homeostasis, blocking the ferroportin-mediated release of iron from enterocytes and macrophages, and impairing the utilization of nutritional or supplemental oral iron. In patients with inflammation, iron release from the reticuloendothelial system is reduced to 44% of that measured in normal subjects[180].

Diagnosis of anemia and ID involves standard laboratory tests (Hb, serum ferritin, TSAT) and blood counts, with low serum Hb or abnormal red blood cell indices usually being the initial finding in a routine complete blood count[5,181]. In some regions, anemic patients should be tested for hemoglobinopathies to exclude genetic reasons for anemia. Since little consensus exists among guidelines on different GI conditions as to the level of anemia that requires follow-up, it has been recommended that any degree of anemia should be further investigated for the presence of ID (Figure 3)[1].

In clinical practice, iron status is mainly assessed on the basis of serum ferritin levels[182]. However, serum ferritin is subject to gender differences and falsely elevated levels in populations with inflammatory reactions since it is also an acute-phase reactant[181]. Therefore, the diagnostic workup of anemic patients (*i.e.*, men with Hb < 13 g/dL or non-pregnant women with Hb < 12 g/dL) should include CRP, to detect underlying inflammatory reactions (suggested cut-off 5 mg/L), and TSAT (suggested cut-off 20%), a marker of low iron availability that is less affected by inflammatory reactions[181,182].

Additional markers of ID include the percentage of hypochromic red cells (%HYPO, suggested cut-off 5%) and the hemoglobin content of reticulocytes (CHr, suggested cut-off 29 pg) as well as serum levels of soluble transferrin receptors (sTfR) and zinc protoporphyrin (ZPP)[17,181]. Since sTfR levels reflect the erythropoietic activity rather than the iron status, sTfR

Table 2 Estimated total iron deficit (mg elemental iron) based on hemoglobin and body weight

Degree of iron deficiency	Hemoglobin level (g/dL)	Iron deficit (mg)	
		Body weight < 70 kg	Body weight ⩾ 70 kg
Moderate	10-12 (women) 10-13 (men)	1000	1500
Severe	7-10	1500	2000
Critical	< 7	2000	2500

Simplified scheme for estimation of total iron requirements[6].

cannot be used in patients treated with ESAs.

Analogous to patients with IBD, iron replacement should also be initiated in non-IBD patients, once IDA is clearly ascertained or deemed likely based on assessed iron markers. Treatment options for IDA include oral and parenteral iron, erythropoiesis-stimulating agents and blood transfusions. There is widespread support for iron supplementation both for the correction of anemia and for replenishment of body iron stores[1]. Currently, the first-line approach for treating IDA is oral iron; usually, 200 mg iron is administered twice daily, but lower doses may be as effective and better tolerated[1]. However, the efficacy of oral iron may be limited when GI uptake is impaired (*e.g.,* due to chronic inflammatory conditions, celiac disease or duodenal resection) or patient compliance is poor (*e.g.,* due to gastrointestinal side effects such as nausea, flatulence and diarrhea[8]). Also large iron deficits that result from chronic or acute GI bleeding or perisurgical blood loss cannot be adequately and quickly counteracted with oral iron. Notably, oral iron can exacerbate existing symptoms of GI disease[4,7], and particularly oral ferrous salts lead to oxidative stress, as evidenced by increased levels of non-transferrin bound iron (NTBI)[183].

Intravenous iron has proven its efficacy and tolerability in a wide range of therapeutic areas, and is recommended in respective treatment guidelines[1,8,127,184-186]. In particular, parenteral iron is considered advisable for patients with GI conditions who cannot be treated adequately with oral iron supplements due to severe GI side effects, inadequate absorption, or anemia requiring urgent correction. Intravenous iron replacement facilitates faster correction of ID and avoids GI side effects by bypassing the GI tract. Although intravenous iron is more costly than oral treatment, administration by a medical professional ensures compliance and more reliable repletion of iron stores which in turn may prevent anemia recurrence and related treatment costs in the long term.

The underutilization of intravenous iron is largely based on past experience with high molecular weight iron dextran (HMWID) that is associated with anaphylactic reactions and therefore has been removed from the market in the United States and Europe. In recent years, safety of intravenous iron has been vastly improved by new, well-tolerated preparations[57,149,187]. A review issued by the United States Food and Drug Administration (FDA) studying serious adverse reactions across different intravenous compounds (iron sucrose, ferric gluconate and low molecular weight iron dextran) showed a cumulative rate of only < 1:200000[188,189]. In 2013, the European Medicines Agency (EMA) published an assessment report[190] concluding that the benefits of intravenous iron-containing medicinal products continue to outweigh the risks in the treatment of iron deficiency when the oral route is insufficient or poorly tolerated. Notably, the EMA removed the necessity of a test dose, yet trained staff and resuscitation facilities to manage anaphylactic or anaphylactoid reactions should be available when any intravenous iron product is administered.

Traditional calculation of iron deficits (iron doses) with the Ganzoni formula is error-prone, inconvenient and underestimates iron requirements[191]. Accordingly, a more simple fixed-dose regimen (of ferric carboxymaltose) based on Hb and body weight (Table 2) was tested in IBD patients, and found to be superior to the Ganzoni-calculated dosing (of iron sucrose) in terms of efficacy and compliance[192]. This novel dosing scheme can equally be utilized as a simple dosing guide for other patient groups and iron formulations that can be given at doses of 1000 mg per administration for efficient and rapid iron replenishment. Most clinical trial and observational data on high dose iron administration have been generated with ferric carboxymaltose and low molecular weight iron dextran. In cases of severe anemia, the iron dose should be increased by 500 mg.

In response to parenteral iron administration, serum ferritin is greatly elevated for the first 8 wk after infusion. Therefore, ferritin should be monitored only after 8-12 wk, and in case of iron overload (TSAT > 50%), treatment should be adjusted accordingly.

Treatment response to intravenous iron replacement can be defined as an increase in hemoglobin levels of ⩾ 2 g/dL within approximately 4-8 wk of infusion and restoration of appropriate iron availability (TSAT ⩾ 30%). Patients who show limited or no response to intravenous iron therapy, especially those with anemia of chronic inflammation, should be considered for adjunctive treatment with ESAs (target Hb level ⩽ 12 g/dL). Overall, intravenous iron replacement is increasingly recommended by gastroenterologists[1,5,8,149].

Regardless of the route chosen, iron therapy must continue after resolution of anemia until iron stores are completely replenished[4]. Once Hb levels and red cell indices have been normalized, they should be monitored at regular intervals[1]. The authors of the British Society of Gastroenterology guidelines propose assessments at 3-monthly intervals for one year, then after a further year, and immediately if symptoms of anemia reoccur[1].

Blood transfusions should be used only as a last

option and as rescue treatment when faced with a life-threatening situation (*e.g.*, in severe cases of acute bleeding)[4,5]. There is a wealth of evidence concerning post-operative mortality and morbidity following blood transfusion, even after transfusion of a single RBC unit[193-195]. Consequently, a restrictive approach to blood transfusion is warranted except for patients who present with ischemic heart disease as pre-existing comorbidity[35,36,195]. In patients with GI disease, transfusions should aim to restore Hb to a safe level, but not necessarily up to normal values, and iron supplementation should be given subsequently to replenish stores[1].

CONCLUSION

IDA is a common comorbidity in patients with GI or liver disorders. In general, the origin of IDA can be multifactorial, with bleeding, malabsorption and inflammation playing important roles in the context of different GI conditions. IDA can contribute substantially to the morbidity and mortality of the underlying disorder and even ID without anemia can reduce quality of life, exercise capacity and cognitive function. Therefore, effective treatment of ID and IDA as well as prevention of recurrence are necessary and may provide an important alleviation of the overall disease burden. The lack of guidelines on diagnosis and treatment of IDA in the field of GI disease results in suboptimal assessment and management of IDA.

The standard laboratory approach used to investigate IDA would benefit from inclusion of TSAT assessment, which is less affected by inflammatory reactions than the commonly-used acute-phase protein serum ferritin.

Oral iron, often selected as the initial treatment option, has considerable limitations in GI patients due to severe GI side effects, inadequate absorption and a slow course of action. Furthermore, patient compliance with oral iron therapy is often poor. If oral therapy fails or is inadvisable, intravenous iron replacement is a valuable option. Intravenous iron therapy is more efficient than oral iron, and faster at increasing Hb levels and replenishing iron stores. Iron therapy should be continued until iron stores are completely replenished. During subsequent follow-up visits for their GI disorder, patients should be routinely monitored for any signs of ID or IDA.

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