Chapter 7

Anemia and IBD: Current Status and Future Prospectives

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Additional information is available at the end of the chapter

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Abstract

Anemia is a common complication of inflammatory bowel disease (IBD), usually recognized at diagnosis and during flare-ups. However, the exact prevalence of anemia associated to IBD (IBD-A) is unknown. Despite its major clinical relevance and quality of life impact in both adult and pediatric IBD patients, it has been for long time neglected. It is mostly multifactorial, being a unique example of the combination of chronic iron deficiency (ID) and anemia of chronic disease (ACD). The current management of IBD-A represents a paradigm shift in clinical practice, involving several challenges. A pro-active approach is recommended and with the new generation of available iron compounds and recent guidelines, the ultimate goal will be the improvement of the patients' quality of life. Sound data are still lacking, concerning the best treatment/prevention approach for IDA/ID. Based on current evidence, oral iron therapy might be preferred in mild IDA, whereas intravenous iron may be advantageous in more severe IDA/flaring IBD. Long-term prospective clinical trials are needed, to optimize treatment schedule and to better define the clinical and hematological long-term outcomes, both in adults and in children. They should demonstrate the efficacy, safety, and tolerance profile of different available iron formulas, as well as their cost-efficacy ratio.

Keywords: anemia, iron deficiency, anemia of chronic disease, inflammatory bowel disease, Crohn's disease, pediatrics, childhood, adulthood

1. Introduction

Anemia is the most common systemic complication and extraintestinal manifestation of inflammatory bowel disease (IBD), particularly in Crohn's disease (CD) patients [1–3]. Although it may be present anytime along the disease course, it is usually recognized at diagnosis and during flare-ups. However, despite its major clinical relevance and quality of life (QoL) impact in both adult and pediatric IBD patients, it has been for long time neglected in this clinical setting [4].

Following the introduction in the last decade of new intravenous (IV) and oral iron therapies, IBD-associated anemia (IBD-A) has been deserving major attention from the scientific community. Furthermore, the increasing focus on extra-digestive features of IBD, in parallel with the recent emergence of specific management guidelines concerning IBD-A from the European Crohn's and Colitis Organisation (ECCO) [5], has also contributed to a paradigm shift in the clinical approach of this clinical entity.

In fact, anemia in IBD is not just a laboratory marker; it is a complication of IBD that requires increased awareness and needs appropriate and timely diagnostic and therapeutic approaches. The impact of anemia on the quality of life of IBD patients is substantial, as it affects several aspects of quality of life, such as physical, emotional, and cognitive functions, work or school absenteeism, hospitalization rate, and health-care costs [4, 6]. Thus, it seems to be reasonable that both in adult and in pediatric IBD patients, anemia should be recognized, comprehensively evaluated, and treated. Furthermore, not only a disease-specific treatment has to be administered but in particular iron-deficiency anemia should be treated, as there is a sound body of evidence demonstrating its beneficial impact in patients' quality of life [4, 6].

2. Prevalence of anemia in IBD setting

The exact prevalence of IBD-A is unknown [3, 4, 6]. Reported prevalence rates of anemia in IBD adult patients widely range from 6 to 74%, depending on the definition of anemia, the study design, the patient population considered (e.g., hospitalized patients versus outpatients), and the standards of screening and treatment [4, 6]. In a recent systematic review, the mean prevalence of anemia in adult patients treated in tertiary referral centers with CD was 27% (95% confidence interval 19–35) and 21% (95% confidence interval 15–27) for ulcerative colitis (UC) [6]. Not surprisingly, anemia is reported more frequently in hospitalized patients with IBD and occurs more frequently in CD as compared to UC. In fact, according to recent published studies, the calculated mean prevalence was 20% among outpatients and 68% among hospitalized IBD patients. Furthermore, women with CD are at a higher risk for anemia. It also appears that hemoglobin (Hb) concentrations increase in the years after diagnosis which may be explained by the remission of disease following successful medical or surgical treatment.

The currently used World Health Organization (WHO) definition of anemia (**Table 1**) applies also to patients with IBD [7–9]. As mentioned in the subsequent text, anemia in IBD is mainly the expression of a mixed pathogenesis with iron deficiency (ID) and anemia of chronic disease (ACD) as the most prominent factors, often coexisting [10]. However, ID is the most frequent cause, with a reported prevalence between 36 and 90% [4, 7]. Recent Scandinavian data in adults indicated the prevalence of iron deficiency anemia (IDA) at 20% and of isolated iron deficiency at 30% (without anemia). After treatment is stopped, IDA has been reported to recur after a 10-month period and iron deficiency after 19 months after treatment [1–4].

Iron deficiency anemia
1. Mucosal inflammation
2. Chronic GI lost
3. Low absorption
4. Poor appetite/malnutrition
5. Dietary restrictions
Anemia of chronic disease
1. Disturbed iron deposit distribution
2. Immuno-mediated modification of iron transportation: iron retention in macrophages; functional iron deficiency: iron deficiency erythropoiesis
3. Inhibition of erythropoietin activity
Drug-induced anemia
1. Differentiation and proliferation inhibition of erythroid progenitor cells
2. Myelosuppressor effect of drugs—direct effect: thiopurines (azathioprine); indirect effect "anti-folic": salazopyrine
3. Sulfasalazine effect: impaired folic acid absorption; hemolysis; medullary aplasia
Vitamin B12 e folic acid deficiency anemia

Table 1. Major causes of anemia in IBD and underlying pathophysiology.

Recognized limitations concerning most studies on the prevalence of IDA in patients with IBD are their retrospective nature or the fact of being surveys from referral centers. Recently, Ott et al. [10] have prospectively assessed the prevalence of IDA in a population-based cohort at the time of first diagnosis and during the early course of the disease. A high prevalence of IDA at different points during the early course of disease was reported. At first diagnosis, anemia of chronic disease was predominant, whereas during follow-up, iron deficiency became the most relevant reason of anemia. These findings are in line with data of other groups [4, 6], also describing a strong association between the severity of anemia and disease activity.

A possible explanation of these findings might be the population-based character of Ott et al. study [10], as not only outpatients of a tertiary referral center were included in this study but also patients with less severe forms of IBD, which are mainly treated by their family doctors. In this setting, reasons for the insufficient response to the treatment might have been underdosing of iron supplementation, subclinical inflammation of the underlying disease, or lack of adherence of the patient. Surprisingly, only in one-third of patients with proven anemia, further diagnostic approach was undertaken. Even patients with diagnosed iron-deficiency anemia were infrequently and inconsequently treated with iron preparations, despite the high impact on quality of life.

Limited previous data suggest that anemia is more prevalent in children than in adults with IBD [7–10], although, to date, there have been no good comparative studies. Although anemia and iron deficiency might be at least as common in pediatric as in adult patients with IBD, the

true prevalence in childhood is not known. In fact, IBD-A has been recently estimated more common (about 70%) in children than in adults (about 30–40%) [10, 11]. In a recent cross-sectional observational study, including pediatric and adult IBD patients, Goodhand et al. [11] found a prevalence of anemia of 70% (41/59) in children, 42% (24/54) in adolescents, and 40% (49/124) in adults ($P < 0.01$). Furthermore, children (88% (36/41)) and adolescents (83% (20/24)) were more frequently iron-deficient than adults (55% (27/49)).

Recent population-based studies have demonstrated that the phenotype of IBD presenting in the young patient differs from that of adult-onset disease [5, 6]. Children and adolescents are more likely to be diagnosed with CD than UC, with a more severe and extensive disease distribution at presentation and more frequent extension of disease during the first 2 years [5, 6]. Since they tend to have more severe IBD, it has been hypothesized that the prevalence of anemia would be predictably greater in children and adolescents than in adults attending IBD outpatient clinics. Although in 2007, Gasche et al. have published the first guidelines on the diagnosis and management of iron deficiency and IBD-IDA [12], only recently the first ECCO guidelines on the management of IDA and ID have emerged. Both guidelines concern IBD-associated anemia, but no specific considerations on the treatment of pediatric IBD patients have yet been included [5, 13].

3. Pathophysiology of anemia

In the majority of cases, IBD-A is mostly multifactorial, being a unique example of the combination of chronic ID and anemia of chronic disease (ACD) (**Table 1**) [4, 5]. Iron deficiency anemia occurs when iron stores are exhausted and the supply of iron to the bone marrow is compromised. IDA is a severe stage of ID in which hemoglobin (or the hematocrit) declines below the lower limit of normal (biochemical evidence of iron deficiency). The precise biochemical definition agreed on by the experts group is given below [5, 7]. In active disease, inflammatory mediators may alter iron metabolism (by retaining iron in the reticular-endothelial system), erythropoiesis, and erythrocyte survival. This condition is termed anemia of chronic disease. Anemia due to iron retention in macrophages driven by pro-inflammatory cytokines and hepcidin is also called functional iron deficiency (FID) [14–16].

Anemia in IBD (an particularly IDA) thus results (a) on the one hand, from low intestinal bioavailability of iron due to chronic intestinal blood loss from inflamed intestinal mucosa; (b) on the other hand, from the combination with impaired iron absorption, either as a consequence of malabsorption and/or short bowel syndrome, or as a consequence of inflammation-driven blockage of intestinal iron acquisition and macrophage iron reutilization; (c) also, impaired dietary iron uptake might be involved, due to therapeutic or voluntary dietary restrictions and anorexia. Among other possible factors, intake of proton pump inhibitors, persisting *H. pylori* infection, may be additionally involved.

Other more rare causes of anemia in IBD include vitamin B12 deficiency (particularly after resection of the ileum), folate deficiency, and potential toxic effects of medications (such as proton pump inhibitors, sulfasalazine, methotrexate, and thiopurines; all these may aggravate

anemia by negatively affecting iron absorption or erythropoiesis [5–7]. In fact, methotrexate and sulfasalazine interfere with the absorption of folate and may mediate folate deficiency [5–7]; sulfasalazine may also induce hemolysis or bone marrow aplasia; thiopurines and methotrexate can induce bone marrow toxicity in a minority of patients. Finally, other causes may include renal insufficiency, hemolysis, and innate hemoglobinopathies [5–7].

The average adult harbors at least 3–4 g of stored iron that is balanced between physiologic iron loss and dietary intake. Most iron is incorporated into hemoglobin, whereas the remainder is stored as ferritin, myoglobin, or within iron-containing enzymes. It is estimated that about 20–25 mg of iron is needed daily for heme synthesis; approximately 1–2 mg of this requirement comes from dietary intake and the remainder is acquired from senescent erythrocytes (recycling) [8, 9]. Total iron loss averages about 1–2 mg/day, mostly via fecal losses, skin, and intestine cellular desquamation, as well as through menstruation.

Body iron homeostasis is finely regulated by multiple and sophisticated mechanisms, the interaction of the liver-derived peptide hepcidin with the major cellular iron exporter ferroportin [15–17] being of major relevance. The synthesis and release of hepcidin are induced by iron loading and inflammatory stimuli such as interleukin 1 (IL-1) or IL-6, whereas its synthesis is blocked by ID, hypoxia, and anemia. Hepcidin targets ferroportin on the cell surface (enterocytes and macrophages), resulting in ferroportin internalization and degradation and blockage of cellular iron entry. Low circulating hepcidin levels enable an efficient transfer of iron from enterocytes and macrophages to the circulation, aiming to overcome ID; on the other hand, iron is retained in these cells when hepcidin levels are high and serum iron levels drop [15–17].

Furthermore, inflammatory cytokines can directly inhibit iron absorption and stimulate the uptake and retention of iron in macrophages via hepcidin-independent pathways. Interestingly, there is clinical evidence that circulating hepcidin levels have an impact on the efficacy of oral iron therapy and can predict its nonresponsiveness; this is consistent with experimental data demonstrating reduced intestinal ferroportin expression and iron absorption in individuals with increased hepcidin levels primarily due to inflammation [17]. As a result, anemia develops and is characterized by low circulating iron levels and an iron-restricted erythropoiesis in the presence of high iron stores in the reticuloendothelial system, reflected by normal or high levels of ferritin.

Hepcidin expression mediated through cytokine and the direct effects of cytokines on iron trafficking in macrophages play a decisive role in the development of this type of anemia (i.e., ACD or the anemia of inflammation), by retaining iron in the reticuloendothelial system and blocking iron absorption, which results in an iron-limited erythropoiesis [15,16]. This is reflected clinically by a reduced transferrin saturation (value below 16–20%). In addition, cytokines and chemokines further contribute to anemia by negatively affecting the activity of erythropoietin and an inflammation-driven impairment of erythroid progenitor cell proliferation [15–17].

As previously mentioned, patients with active IBD may have true ID due to chronic blood loss, as reflected by low ferritin levels. Moreover, true ID and anemia reduce hepcidin expression. These effects drive an iron-deficiency-mediated inhibition of SMAD signaling in hepatocytes and

erythropoiesis-driven formation of hepcidin inhibitors such as erythroferron and growth differentiation factor 15 (GDF-15) [15, 16]. Thus, in the presence of both inflammation and true ID, circulating hepcidin levels decrease because inflammation-driven hepcidin induction is largely regulated by anemia and ID. Therefore, in truly iron-deficient patients, despite the presence of systemic inflammation, considerable amounts of iron might still be absorbed from the intestine.

4. Diagnostic criteria and differential diagnosis

As stated, in IBD patients, anemia is often multifactorial, being IDA, the most common cause. ACD is also an important etiology, and usually is associated with poor disease control or severe disease. Other causes contributing to anemia in IBD include vitamin B12 and folic acid deficiency as well as adverse effects of certain drugs (salazopyrine sulfasalazine and azathioprine). In both adult and pediatric patients with IBD, other chronic conditions should also be considered (i.e., renal insufficiency, hemolysis, and innate hemoglobinopathies).

In pediatric-IBD setting, other mechanisms of IDA, non-IBD related, must be considered, as this is a high-risk group of ID and IDA, namely characterized by high growth periods, insufficient ingestion due to dietetic choices, parasitic infestations, low socioeconomic level, and migrant families. It should also be noticed that ID in the absence of anemia is more common than IDA, as normal Hb levels do not necessarily mean adequate iron stores [5, 7].

World Health Organization anemia definition (**Table 2**) is considered valid in both adult and pediatric patients with IDA and current ECCO guidelines recommend its application to the establishment of anemia diagnosis.

Hemoglobin levels are influenced by age, gender, pregnancy, ethnicity, altitude, and smoking habits. Interpretation of Hb and hematocrit levels should take these factors into account.

All patients with IBD should be screened regularly for anemia, especially in the presence of active disease, as ACD can coexist with IDA. The initial workup to establish anemia diagnosis (and to differentiate IDA from ACD) should include complete blood count, C-reactive protein (C-RP) or erythrocyte sedimentation rate (ERS), serum ferritin, and transferrin saturation. A mean corpuscular volume (MCV) and reticulocytes are also helpful in the classification and differential diagnosis of anemia in IBD setting (**Table 3**). In some situations, microcytosis and macrocytosis may coexist, neutralizing each other and resulting in a normal MCV. In this case, a wide size range of the red cells (red cell distribution width) (RDW) is an indicator of ID, further contributing to the differential diagnosis. Platelet and white blood cell counts, also available within the complete blood count, are important to distinguish isolated anemia from pancytopenia.

By definition, IDA presents as anemia associated with low serum ferritin (referred as the most important laboratory parameter in the definition of IDA), low serum iron, low transferrin saturation, and elevated total iron-binding capacity. Other hematological parameters, such as RDW, mean corpuscular volume, and mean corpuscular hemoglobin (MCH), might also contribute to IDA diagnosis; high RDW, low MCV, and MCH corroborate IDA. These parameters

Age/gender	Hb (g/dL)	Ht (%)
6 months to 5 years	11.0	33
6–11 years	11.5	34
12–13 years	12.0	36
Female ≥14 years non-pregnant	12.0	36
Female ≥14 years pregnant	11.0	33
Male ≥14 years	13.0	39

Table 2. Minimum Hb and hematocrit (Ht) levels according to age and gender use for anemia definition (WHO) [9].

Microcytic anemia with normal or low reticulocytes
Iron deficiency anemia, anemia of chronic disease, hereditary microcytic anemia, lead poisoning
Microcytic anemia with elevated reticulocytes
Hemoglobinopathies
Normocytic anemia with normal or low reticulocytes
Anemia of chronic disease, acute hemorrhage, renal disease anemia, aplastic anemia, pure red cell aplasia, primary bone marrow diseases, bone marrow infiltration by cancer, combination of iron deficiency, and B12/folate deficiency
Normocytic anemia with elevated reticulocytes
Hemolytic anemia
Macrocytic anemia with normal or low reticulocytes
Myelodysplastic syndrome, vitamin B12 deficiency, folate deficiency, long-term cytostatic medication, hypothyroidism, alcoholism thiamine-responsive megaloblastic anemia syndrome
Macrocytic anemia with elevated reticulocytes
Hemolytic anemia, myelodysplastic syndrome with hemolysis

Table 3. Classification of anemia by MCV and reticulocytes (adapted from Refs. [5, 7]).

may be normal in ACD. In the presence of inflammation (such as acute exacerbation or poorly controlled disease), it should be recognized that ferritin levels are usually high. New promising markers, such as a soluble form of transferrin receptor (elevated in iron deficiency despite the presence of inflammation) are particularly helpful in the presence of active disease, being currently available in some centers [17]. Other markers, such as serum hepcidin and red blood cell size factor, may further contribute to differential diagnosis of IDA and ACD [15, 16].

Currently, it has been proposed that, in the absence of inflammation/active disease, serum ferritin levels of <30 μg/L reflect depleted iron stores; during active disease, serum ferritin levels of <100 μg/L should be considered as depleted iron stores. In both settings, transferrin saturation of <16% has been associated with poor iron stores. IDA should be considered in the presence of elevated inflammation parameters and normochromic and normocytic anemia or microcytic and hypochromic anemia with serum ferritin of >100 μg/L.

If, after initial workup, the cause of anemia remains unclear, other tests should be performed according to the most plausible cause of anemia, such as determination of serum B12 vitamin, folic acid, blood smear, haptoglobin, lactate dehydrogenase, urea, creatinine, and electrophoresis of Hb [5].

5. Evolving treatment strategies

5.1. Treatment goals and options

The treatment strategies of IDA in IBD both in adult and in pediatric patients are evolving from an expectant approach, which is no longer acceptable, to a more interventive approach. A pediatric retrospective study [13] including 80 children with active IBD and IDA evaluated the hematological recovery associated with an expectant management (for a median period of 12 weeks, in parallel with induction therapy). The authors concluded that this approach caused only a modest increase in hemoglobin levels, and that the proportion of children with exclusive IDA had increased within the follow-up period.

In adult IBD setting, the available evidence also supports an interventive attitude as having better outcomes. In one retrospective population-based cohort study [11] (with 279 both adult and pediatric IBD patients: 183 CD, 90 UC, and six indeterminate colitis) that aimed to assess the prevalence of anemia at first diagnosis and during the early course of the disease (during the 5 years of study period), anemia was found at any time during the study time in 90/279 patients (32.2%). At the time of initial IBD diagnosis, 68 patients were anemic (75.5% of all patients with anemia) and 44 patients develop anemia at the first year. IDA was found in 63 (70%) of 90 patients (all anemic patients) and 26 (38.2%) of 68 anemic patients with anemia at diagnosis and in 27/44 patients at 1 year after diagnosis. Considering IDA treatment, only nine patients with IDA at diagnosis (35%) received iron therapy and 18 patients with anemia at 1 year after diagnosis. Overall, considering the study period, only 32 patients with IDA at any time of the study received iron treatment (IV iron was only prescribed in five patients) and 38 remaining patients with IDA did not receive any treatment. The authors concluded that despite the high prevalence of IDA during the early course of disease and the potential highly negative impact on the quality of life, the treatment was infrequent and inconsequent.

IDA and ID without IDA are associated with poor quality of life that is independent of IBD clinical activity [5, 7, 18]. Several studies document that IDA treatment is associated with better outcomes in quality live assessment [5, 7, 18]. Thus, currently, IDA treatment is a formal recommendation in IBD patients, reflected by the recent ECCO guidelines [5]. The goal of iron supplementation is to normalize hemoglobin levels and iron stores. Current treatment options, in IBD-associated IDA, include both oral and IV iron formulas [5, 19–21] (**Table 4**).

The ECCO guidelines recommend IV iron as first-line treatment in patients with clinically active IBD, with previous intolerance to oral iron and Hb below 10 g/dL, as well as in patients who need erythropoiesis-stimulating agents [5]. These guidelines consider that IV iron is a

good treatment option in IDA-IBD patients, as it has demonstrated to be more effective, better tolerated, and to improve quality of life to a greater extent than oral iron supplements. Recently published ECCO guidelines, however, do not take into consideration the pediatric age group and no specific considerations are made considering this age group [5].

Oral iron is available as inorganic ferrous salts, the daily dose ranging between 50 and 200 mg, in adults and 3–5 mg/kg/day up to 100 mg/day in pediatric patients (**Table 4**). Although oral iron supplementation has been traditionally used in IBD patients (adult and pediatrics) in the presence of IDA, IV iron, however, is rapidly becoming the first line of treatment in this setting, mainly based on efficacy data, convenience of administration (especially with the most recent formulations—**Table 4**), and good safety profile [23–28]. At present time, there are several available formulations for this purpose, as previously mentioned [5, 19–22]. At pediatric age, IV formulas currently approved by Food and Drug Administration (FDA) and by European Medicines Agency (EMA) are expressed in **Table 4**.

Regarding dosage of IV iron, Ganzoni's formula [29] [(body weight in kg × [target Hb-actual Hb in g/dL] × 0.24 + 500)], has been used to calculate iron dosage, both in adult and in pediatric patients. However, the formula is complex, difficult to use in clinical practice, and appears to underestimate iron requirements. Alternatively, a simple scheme (**Table 5**) has been proposed in the FERGIcor study (*Note: FERGIcor has no additional definition, as it is the specific name/designation of a randomized controlled trial on ferric carboxymaltose for iron deficiency anemia in IBD*) [25], in which the estimation of IV iron need is based according to pretreatment Hb level and body weight. Although initially used only to calculate FCM dosage, it has currently been used in other IV iron formulations, and is recommended in the ECCO guidelines. Limitations of this scheme include lack of validation in pediatric patients with bodyweight of <35 kg and patients with Hb below 7.0 g/dL, who may require an additional 500 mg. Also, the estimation of iron needs in ID without anemia is not taken into account.

5.2. Efficacy, safety, and tolerance data

The efficacy and safety of IV iron for the treatment of IDA in IBD adult patients is well established and demonstrated by several studies [23–28]. However, evidence regarding the superiority of IV iron versus oral formulas is yet to be proven [30–33]. In fact, there are several studies and systematic reviews comparing oral and different IV formulas, with variable results considering efficacy in improving Hb levels, tolerance, and safety (related to common severe adverse effects) [4, 6]. Particularly in adult IBD patients, data from large published trials are available, concerning iron sucrose (IO), ferric carboxymaltose (FCM), and iron isomaltoside (IS) [6, 23, 24, 26–28].

The first IV formulas (high-molecular-weight iron dextran (HMW ID) were associated with more frequent and severe side effects (anaphylactic reactions), as a consequence of IV iron. It has been initially used in specific settings, such as chronic kidney disease, neoplastic, and gynecologic diseases. In gastroenterological disease, IV iron was traditionally reserved for patients with intolerance or inadequate response to oral iron and/or in whom a rapid increase in iron stores was desired. As new IV iron formulas developed, composed by strongly bound

Products						
IV formulations	**Low Mw* iron dextran (CosmoFer®)**	**Iron gluconate (Ferrlecit®) hemodialysis patients**	**Iron sucrose (Venofer)**	**Iron carboxymaltose (Ferinject®)**	**Ferumoxytol (Feraheme®)****	**Iron isomaltoside 1000 (Monofer®)**
Carbohydrate molecule	Dextran (branched polysaccharides)	Gluconate (monosaccharides)	Sucrose (disaccharides)	Carboxymaltose (branched polysaccharides)	Carboxymethyl dextran (branched polysaccharides)	Isomaltoside 1000 (unbranched linear oligosaccharides)
Complex stability	High	Low	Moderate	High	High	High
Maximum single dose	20 mg/kg Single dose; limit 200 mg	125 mg	200 mg	20 mg/kg Single dose; limit: 1000 mg	510 mg	20 mg/kg
Infusion within 1 h	No	NA	NA	Yes	Yes	Yes
Test dose required	Yes	No	Yes/no	No	No	No
Iron concentration (mg/mL)	50	12.5	20	50	30	100
Vial volume (mL)	2	5	5	2 and 10	17	
Pediatric use/data available	No	Yes (in chronic renal disease) Dosage in 0.12 mL/kg. (maximum dosages 125 mg per dose)	Yes (maximum dose per administration 5–7 mg/kg)	Yes (approved > 14 years old)	No	No
Oral formulations						
Ferric hydroxide-polymaltose, iron sulfate (oral solutions 100 mg/5 ml and tablets 50 mg; 100 mg; 200 mg) approved in pediatric patients (3–5 mg/kg/day up to 100 mg/day)						
Ferric maltol (30 mg hard capsules): dosage 30 mg bid, no data available in pediatric population, 12-weeks treatment required, it should not be used in patients with IBD flare or in IBD-patients with Hb <9.5 g/dL [22]. www.ema.europa.eu/docs/en_GB//WC500203503.pdf						

*Mw, molecular weight.

** Only approved in United States of America (USA).

Table 4. Main characteristics of oral and IV iron formulations available (adapted from Refs. [5, 19–22]).

Hb (g/dL)	Bodyweight 35–70 kg	Bodyweight ≥70 kg
10–12 (female)	1000 mg	1500 mg
10–13 (male)	1000 mg	1500 mg
7–10	1500 mg	2000 mg

Table 5. Simplified scheme to estimate IV iron dosage [5, 7].

iron carbohydrate complex (an iron core is wrapped in a carbohydrate shell), in order to minimize the potential risk of free iron reactions and the high immunogenicity leading to severe adverse reactions of the oldest IV iron formulas, IV iron is becoming a more frequent treatment option in IBD setting. These new formulas largely replaced the use of iron dextrans, as they have better safety profiles (allowing the administration without the need of a test dose), and also allowing a more time-efficient fashion in a single high-dose infusion. Nevertheless, iron reactions may occur with all IV iron preparations, but they are generally not thought to be immune mediated [30–33].

Each IV formula has a different profile of side effects, being the most common hypotension, tachycardia, stridor, nausea, dyspepsia, diarrhea, and skin flushing. Other described side effects include itching, dyspnea, wheezing, and myalgias (especially in the infusion of large-molecule iron complexes); however, it should be referred that an acute myalgia at the first administration of IV (without any other symptoms) that alleviates spontaneously within minutes (i.e., the so-called *Fishbane reaction*) usually does not recur, and rechallenge is unnecessary. Serious side effects are rare and include severe allergic reactions, anaphylactic shock, and cardiac arrest, but such problems are more common with the older IV formulas mostly dextran-containing preparations [30–33].

The new IV iron compounds FCM and IS are currently approved for use in IBD setting in Europe and ferumoxytol in the United States. All three compounds have showed high stability, favorable safety profile, and complete replacement of total doses of iron in 15 min [24–27]. FCM was the first of the new agents to be approved for more rapid administration of large doses. FCM can be administered as an infusion of 500–1500 mg in 15 min; however, it allows only doses up to 1000 mg per single dose. This IV iron formula is approved in both adult and pediatric patients (age >14 years old). IS is a particularly promising IV iron formulation, as it can be administered in high doses with a maximum single dosage of 20 mg/kg body weight, allowing single administration of iron doses exceeding 1000 mg. However, it is only approved in adult patients. In younger pediatric patients (<14 years old), IS is the only approved formula.

In 2013, Gasche et al. [7] recommended that oral iron should be considered a possible treatment options in patients with mild to moderate anemia (Hb ≥10 g/dL, ferritin <30 μg/L), as oral iron formulations have low cost and are administered at home. Current published ECCO guidelines reinforce this recommendation, as they suggest that oral iron is effective in patients with IBD and may be used in patients with mild anemia, whose disease is clinically inactive and who have not been previously intolerant to oral iron.

Nevertheless, though several studies (including adult and pediatric patients) have demonstrated the effectiveness of oral iron formulas in reestablishing normal hemoglobin levels, these compounds have a slow response in Hb levels (as it may take until at least 2 months to achieve the desirable Hb level, and up to 6 months to reestablish adequate iron stores), poor gastrointestinal tolerance (especially if high doses are required), poor absorption (in active disease and in the presence of inflammation iron absorption is further limited due to inflammation-driven blockade as referred before), and low compliance (compromising the treatment goal). Intolerance to oral iron therapy leading to discontinuation has been reported to be as high as 20% [7, 23, 24].

Additionally, there is some evidence in animal model [34] that oral iron might contribute to deterioration of mucosal injury. Furthermore, as absorption of iron from the gastrointestinal tract is limited, the unabsorbed iron is exposed to the ulcerated intestinal surface. One animal model study [35] compared the effect of oral versus IV formulas on inflammatory and oxidative stress markers in colitis induced in rats. The animals were divided in four groups (one healthy control, one colitis-induced control), two of the three colitis rats received 5 mg iron/kg of body weight a day (as oral or IV iron) for 7 days. Histologic and laboratory inflammatory markers were assessed. The authors found that the oral iron-treated group had a significant worsening of histologic and inflammatory markers, as compared with the IV iron treatment group and the two control groups. They proposed that IV iron should be considered in IBD patients, as it has shown negligible effects on systemic oxidative stress and local or systemic inflammation.

Other feature that has negatively influenced the option of treatment with oral iron is the putative reported increased prevalence of intestinal adenomas associated to prolonged oral iron treatment, in murine colitis model [30, 32, 33]. However, the true impact of oral iron on mucosal injury in IBD patients is not well established and the potential risk of colorectal carcinoma in humans remains controversial [36]. So far, these potential adverse effects of oral iron could not be confirmed in several published trials [30, 32, 33]. Only one human study specifically assessed this question [37]. In a small study including 10 CD patients with active disease and 10 healthy controls treated with ferrous fumarate for 7 days, the Crohn's Disease Activity Index (CDAI), gastrointestinal complaints and blood samples for antioxidant status, anemia, inflammation, and iron absorption were evaluated (on days 1 and 8). The authors found an increase in CDAI, and patients reported an increase in diarrhea, abdominal pain, and nausea at day 8; moreover, a deteriorated plasma antioxidant status in CD patients as compared with controls was observed, thus suggesting that oral iron treatment deteriorated plasma antioxidant status and increased specific clinical symptoms in patients with active Crohn disease. However, these data should be interpreted with caution, as it was a small sample, referring to a group of patients in which oral iron was not recommended, according to past and current guidelines.

Another potential negative effect of oral iron is the modification of the gut microbiome. In one recent open-labeled clinical trial, the effects of oral (iron sulfate) versus IV iron (Iron sucrose) over a 3-month period, in adult patients with IBD (CD: 31; UC: 22) versus control subjects with IDA without inflammation and its impact in clinical parameters, gut microbioma, and metabolome [38] were compared. The authors concluded that both oral and IV iron were

effective in the correction of Hb levels, and moreover they found that oral iron distinctively affected bacterial phylotypes and fecal metabolites, as compared to IV iron. Although these data should take into consideration that IBD patients have already a disturbed gut microbioma, they highlight the potential additional gut damage of oral iron.

A recently published prospective controlled open-label 6-week non-inferiority trial, including 45 adolescents (aged 13–18 years) and 43 adults (>18 years) with IBD, aimed to assess the effects of oral iron (ferrous sulfate) on Hb level, disease activity (clinical scores and inflammatory parameters—fecal calprotectin and CRP) and also the relationship between baseline serum hepcidin and Hb response [39]. Quality of life was also evaluated. Rampton et al. [39] found that the effectiveness (improvement in Hb level) and tolerance of oral iron were similar in both age groups, and an inverse relationship between Hb response and baseline Hb, CRP, and hepcidin was observed. Also, the disease activity was not affected by oral iron and patients reported an improved quality of life—short IBD questionnaire (IBDQ) and perceived stress questionnaire scores in adults. The authors concluded that oral iron was effective in IDA treatment and that CRP and that hepcidin levels at baseline could be used as additional markers to better decide whether iron should be given orally or IV.

Ferric maltol is a novel oral ferric iron compound, associated with a lower rate of gastrointestinal effects, with potential use to treat iron deficiency anemia in mild-to-moderate IBD, even in those who are intolerant to oral ferrous products [40]. This clinical benefit has the potential to change treatment pathways and increase treatment options. Currently, this compound is only approved in adult patients.

In the last decade, numerous studies aimed to compare oral and IV iron treatment options, regarding safety, tolerance and efficacy, as well as impact in the quality of life [23–28, 41]. There are several published systematic reviews in this subject, as well as single and multicenter studies. All the main IV iron formulations have been compared with oral compounds. However, studies comparing different new IV iron formulas among each other and comparing traditional oral iron with the new formulations are lacking. Also, most data refer to adult IBD population; pediatric evidence, although scare, is emerging.

Considering the studies comparing oral iron sulfate to most used IV formulas (IS, FCM, and II) in IBD adult patients, the published data highlight that all IV formulas are safe, well tolerated, and effective in achieving desirable Hb levels. The superiority of IV versus oral iron in treating IDA-IBD remains unclear, as different results have been published. Studies have found, however, that treatment discontinuation due to adverse events was lower in patients treated with IV iron, as compared to patients treated with oral iron. These data are reflected in the current ECCO recommendations (mentioned previously), as oral iron is still a treatment option.

In the IS versus oral iron trial [23], a randomized 20-week, controlled, evaluator-blind, multicenter study with 91 adult patients with IBD and anemia (Hb <115 g/L), the authors reported that IV iron was more effective in correcting hemoglobin and iron stores, when compared to oral iron. In the oral iron group, only 48% tolerated the prescribed dose (which might had influence in the final result in terms of achieving normal Hb levels).

The FCM versus oral iron multicenter study trial [24] (including 200 adult IBD; follow-up of 12 weeks) attested the safety and effectiveness of FCM IDA-IBD. Although in this study, FCM allowed fast Hb increase and adequate iron stores, it could only demonstrate the non-inferiority of this IV iron formulation in terms of Hb change over the study time. Also, the rate of adverse effects was similar in both iron formulas.

Finally, the IV versus oral iron study, published by Reinisch et al. [28], was a randomized, open-label trial with a total of 338 adult IBD patients in clinical remission or with mild disease and an Hb of <12 g/dL. They aimed to prove the non-inferiority of IV iron when compared to oral iron regarding the correction of IDA, as well as to document the number of patients who discontinued the study because of lack of response or intolerance of investigational drugs, change in total quality of life, and safety. This study could not demonstrate the non-inferiority in changing Hb at week 8 post treatment. Indeed, there was a trend for oral iron sulfate being more effective in increasing Hb than IV. The authors suggested that the results might have been influenced by the underestimation of true iron needs by the Ganzoni formula.

Two systematic reviews and meta-analysis of iron replacement therapy in IBD patients with IDA recently published compared the efficacy of oral versus iron therapy in the treatment of IDA in adult IBD patients [21, 30]. One review identified 757 articles. The total sample size included 333 patients, with 203 patients receiving IV iron treatment. The primary outcome was the mean change in the hemoglobin and secondary outcomes included the mean change in ferritin, clinical disease activity index, quality of life score, and the adverse reaction rate. The authors concluded that IV iron is better tolerated and more effective than oral iron treatment in improving ferritin levels. Another systematic review published in 2013 [30], including again only adult IBD patients, also highlighted that IV iron was the best option to the treatment for IDA-IBD, due to improved Hb response, no added toxicity, and no negative effect on disease activity, when compared with oral iron replacement.

The most recently published systematic review, including only evidence from randomized controlled trials [33] (five studies including 694 adults with IBD), and comparing IV versus oral iron, also concluded that IV iron appears to be more effective and better tolerated than oral iron for the treatment of IBD-associated anemia, as IV iron presented higher efficacy in achieving a hemoglobin rise of ≥2.0 g/dL, lower treatment discontinuation rates due to intolerance or adverse effects (including lower gastrointestinal adverse events).

In pediatric patients with IBD-associated IDA, the evidence concerning the different treatment strategies, namely the use of IV iron formulas, is still scare. Also, as previously mentioned, only IS and FCM IV iron formulations are currently approved, wherein FCM is only recommended in pediatric patients of >14 years old (**Table 4**). In the pediatric IDA-IBD setting, so far three published studies support the efficacy of available IV iron formulas [11, 41, 42]. In these studies, both IS and FCM were used and showed to be equally effective in the treatment of IBD-IDA, achieving both the desirable Hb level and adequate iron stores in most patients.

In a small single-center prospective study, including 19 pediatric CD patients (median age: 15.5 years) with remissive/mild disease, with a follow-up of 40 months, Azevedo et al. [41] evaluated the safety and efficacy (short and long term) of IV iron, as well as the need of re-treatment.

The median Hb before and after IV iron was 10.5 and 12.7 g/dL, respectively. No major adverse reactions were documented. This prospective study thus emphasized the efficacy and safety of IV iron in pediatric IBD patients. In a retrospective study, Laass et al. [42] reported the treatment of pediatric patients with IDA associated to several gastrointestinal disorders, including a subset of 52 IBD patients (29 CD patients) with a mean age of 11.8 years. In this pediatric study, all patients were treated with FCM, and the mean Hb level after treatment of 11.9 g/dL was achieved, with good tolerance and minor side effects. In this study, FCM showed efficacy and a good safety profile, although data concerning the disease activity and long-term follow-up of the patients were not reported.

The safety and effectiveness of IV iron (IS) in the pediatric setting were also recently reported in another prospective single-center study (conducted in 24 children with IBD treated with infliximab) [43]. In this study, IS was administered after infliximab and no adverse reactions were documented.

6. Prevention

The recurrence of IDA in IBD is well recognized, occurring in about 50% of the adult patients within 10 months after IV iron treatment [5, 7, 44, 45].

Recurrence of IDA is directly related with iron replenishment at the end of IV iron treatment [5, 44–46]. It is admitted that ferritin levels over 400 μg/L might prevent recurrence of IDA in the subsequent 1–5 years.

ECCO guidelines state that IBD patients should be monitored for recurrent iron deficiency every 3 months for at least 1 year after correction, and between 6 and 12 months thereafter [5]. Furthermore, they highlight that recurrence might be associated to persistent intestinal disease activity even if there is clinical remission and remission in inflammatory parameters. An important message is that recurrence of anemia, especially in the setting of ACD, should lead to the evaluation of disease activity and an optimized treatment strategy would be required, as disease control is usually sufficient to correct anemia.

Data concerning recurrence of IDA in pediatric patients are scarce; however, considering the high prevalence of pediatric IBD-IDA anemia, a recurrence rate similar to that reported in adult patients should be expected. So far, these data were only described in one study [41], in which six of 19 (30%) patients needed re-treatment within the 40 months of follow-up (median period of 15.5 months). Re-treatment was proposed when Hb levels fell under the baseline level according to WHO criteria and after excluding other factors than IDA contributing to anemia. This study reinforces the importance of long-term follow-up of the iron status, also in pediatric CD patients.

The most recent ECCO guidelines suggest that after IV iron treatment, re-treatment should be initiated as soon as serum ferritin drops below 100 μg/L or Hb drops below cutoff level according to WHO criteria [5]. However, the benefit evidence of treating iron deficiency in the absence of anemia in IBD patients and particularly in pediatric IBD patients is yet unavailable. Currently,

there are no guidelines concerning the management of ID without anemia in both adult and pediatric IBD patients. However, ID without anemia and IDA should be closely monitored.

The rational of preventing IDA by treating ID relies on the fact that iron is important to cell function and that ID can cause symptoms with a negative impact on the quality of life [5, 18]. Several symptoms have been associated to ID, such as reduced physical performance and cognitive function, fatigue, headache, sleeping disorders, loss of libido, or restless-legs syndrome among others [47].

The evidence concerning the treatment of ID without anemia in the IBD setting, however, is not yet available. ECCO guidelines recommend that the choice of treating ID without anemia should be considered on an individual basis (according to patients' past medical history and comorbidities, age group, symptoms, and individual/parental preferences) [5]. Data on the effectiveness of periodic IV iron administration as a prevention of IDA in IBD patients are available for FCM and II (in adult patients) [44–46]. In the adult studies, after IDA treatment with IV iron, patients received regular doses of IV iron (300–500 mg of FCM or II) during a 12-month period allowing to maintain stable Hb levels without IDA recurrence and with good tolerance regarding side effects.

In refractory cases of ACD with an insufficient response to intravenous iron and despite optimized IBD, therapy ECCO guidelines propose that these patients may be considered for erythropoiesis-stimulating agent treatment. The recommendation is supported by studies demonstrating the improvement of Hb levels; follow-up data, however, are lacking and these agents should be used with caution [5]. There are no pediatric data on the use of erythropoiesis-stimulating agents in IBD patients.

Red blood cell transfusion may be considered when Hb concentration is below 7 g/dL, or above if symptoms or particular risk factors are present. ECCO guidelines also recommend that blood transfusions should be followed by subsequent intravenous iron supplementation [5].

7. Final comments and future prospectives

In conclusion, the current management of IBD-A represents a paradigm shift in clinical practice, involving several specific challenges. A pro-active approach is recommended, and both adult and pediatric IBD patients should be regularly assessed for the presence of anemia, because of its high prevalence, impact on quality of life, and comorbidity.

Although both oral and IV formulations have demonstrated efficacy in IBD-A, oral iron might not be an ideal treatment for active IBD-A, with gastrointestinal intolerance occurring in many patients and a long course needed to resolve anemia and replenish stores. Nonadherence to a prescribed course of oral iron is common, and even in adherent patients, poor intestinal absorption fails to compensate for iron need in the presence of ongoing blood losses. In addition, studies in animal models do not exclude the possibility that oral iron formulations might increase disease activity in IBD and even the risk of development of colorectal cancer.

IV iron treatment has shown to be safe and well tolerated in IBD patients with good clinical response in different formulations (prolonged response). However, although the safety of IV iron has been demonstrated in studies comprising thousands of patients with numerous clinical entities associated with ID, safety concerns still exist. All iron products can cause hypersensitivity or other reactions and the comparative frequencies of reactions remain unknown. All involved clinicians should acquaint with the incidence, clinical nature, and significance of reactions to the existing preparations, systematically reporting to a central agency.

Although any IV iron can cause acute severe reactions, the incidence and severity of reactions seem quite low, with the doses commonly administered in clinical practice and currently available dextran-free formulations of intravenous iron (as iron gluconate, IO, and FCM). Similarly, concerns about IV iron therapy potentially increasing the risks for infections and cardiovascular disease have not been confirmed in prospective studies or clinical trials and remain largely unproven hypothesis. There remain, however, some concerns about the potential for long-term harm from repeated iron administration.

Sound data are still lacking, on when to stop iron supplementation therapy in order to avoid iron overloading, which may cause side effects, because of the potential of the metal to catalyze the formation of toxic radicals. Recent guidelines on the management of anemia in dialysis patients suggest that ferritin levels of up to 500 ng/mL appear to be safe and this limit might be a useful upper threshold in the management of patients with IBD-A. Interestingly, in a recently published prospective single-center study, iron supplementation in chronic kidney disease patients was associated with a significant reduction in overall mortality.

Certainly, the control of inflammation is a key objective in the treatment of IBD. Because IDA has a considerable impact on patient quality of life, a thorough and complete diagnostic and therapeutic strategy should be followed to help patients attain as normal a life as possible. Given the novel intravenous iron-replacement regimens introduced within the last 10 years, physicians may have some doubts concerning the optimal iron-replacement regimen to be prescribed. Based on the current evidence and guidelines, oral iron therapy should be preferred for patients with mild IDA in quiescent disease stages unless they are intolerant or have an inadequate response, whereas IV iron supplementation may be advantageous in patients with more severe IDA or flaring IBD, because inflammation compromises intestinal iron absorption.

Further well-designed clinical trials, including well-selected patients and clearly detailing primary and secondary outcomes, are warranted, to optimize the treatment schedule in these patients. In particular, considering the small number of published randomized controlled studies in this important area, prospective studies will be necessary to establish the optimal dose for correction and maintenance of target Hb levels and iron stores (definition of clinical end point) and to clarify the impact of anemia correction and iron supplementation on the course of IBD-A and patient outcomes. Ideally, these clinical trials should integrate new surrogate biomarkers, reflecting more precisely the true systemic iron pathways.

Also, prospective clinical trials are needed to better define the clinical and hematological long-term outcomes in patients with IBD-A. In fact, good-quality data are required both in adults

and in children, demonstrating the efficacy, safety, and tolerance profile of different available iron formulas (oral and IV) in IBD-IDA, as well as to determine their cost-efficacy ratio.

The importance of long-term follow-up of the iron status in IBD patients, including in those in remission and/or with mild disease, should also be emphasized, as well as the inclusion of quality of life impact as a relevant specific intervention outcome. Finally, the future acquisition of larger pediatric experience in the field will drive the emergence of evidence-based-specific pediatric guidelines.

In summary, all clinicians (particularly gastroenterologists) treating patients with IBD will need to be increasingly aware of the importance of the screening, diagnosis, and management specificities of anemia and IBD, for improvement in their general well-being, a matter which frequently does not yet gain the required attention. With the new generation of available iron compounds and existent guidelines, the ultimate goal will be the improvement of the patients' quality of life.

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