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Management of Iron-Deficiency Anemia in Inflammatory Bowel Disease

A Systematic Review

Ole Haagen Nielsen, MD, PhD, Mark Ainsworth, MD, PhD, Mehmet Coskun, MSc, PhD, and Günter Weiss, MD

Abstract: Anemia is the most frequent complication of inflammatory bowel disease (IBD), but anemia, mostly due to iron deficiency, has long been neglected in these patients.

The aim was to briefly present the pathophysiology, followed by a balanced overview of the different forms of iron replacement available, and subsequently, to perform a systematic review of studies performed in the last decade on the treatment of iron-deficiency anemia in IBD.

Given that intravenous therapies have been introduced in the last decade, a systematic review performed in PubMed, EMBASE, the Cochrane Library, and the websites of WHO, FDA, and EMA covered prospective trials investigating the management of iron-deficiency anemia in IBD published since 2004.

A total of 632 articles were reviewed, and 13 articles (2906 patients) with unique content were included. In general, oral supplementation in iron-deficiency anemia should be administered with a target to restore/replenish the iron stores and the hemoglobin level in a suitable way. However, in patients with IBD flares and inadequate responses to or side effects with oral preparations, intravenous iron supplementation is the therapy of choice. Neither oral nor intravenous therapy seems to exacerbate the clinical course of IBD, and intravenous iron therapy can be administered even in active disease stages and concomitantly with biologics.

In conclusion, because many physicians are in doubt as to how to manage anemia and iron deficiency in IBD, there is a clear need for the implementation of evidence-based recommendations on this matter. Based on the data presented, oral iron therapy should be preferred for patients with quiescent disease stages and trivial iron deficiency anemia

unless such patients are intolerant or have an inadequate response, whereas intravenous iron supplementation may be of advantage in patients with aggravated anemia or flares of IBD because inflammation hampers intestinal absorption of iron.

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Abbreviations: ACD = Anemia of chronic disease, CD = Crohn's disease, CRP = C-reactive protein, EMA = European Medical Agency, FDA = US Food and Drug Administration, Hb = Hemoglobin, IBD = Inflammatory bowel disease, IDA = Iron-deficiency anemia, IL = Interleukin, kDa = Kilo Dalton, MCV = Erythrocyte mean cell volume, MCHC = Erythrocyte mean cell hemoglobin concentration, MRI = Magnetic resonance imaging, TFN = Tumor necrosis factor, TSAT = Transferrin saturation, UC = ulcerative colitis.

INTRODUCTION

Anemia is the most common complication of inflammatory bowel disease (IBD)^{1,2} both at diagnosis and during flare-ups,^{3,4} exceeding by far the frequency of extraintestinal manifestations (eg, rheumatic, dermatologic, and ophthalmologic).^{5,6} Thus, in a systematic review from 2014 the prevalence of anemia in patients treated in tertiary referral centers with Crohn disease (CD) was 27% (95% confidence interval 19–35), and 21% (95% confidence interval 15–27) for ulcerative colitis (UC).¹ This huge variation may be due to differences in the study populations (eg, hospitalized patients vs. outpatients) as well as in the definition of anemia. In recent published studies of IBD patients, the calculated mean prevalence was 20% among outpatients⁷ and 68% among hospitalized patients.⁸ Furthermore, anemia is more common in CD than in UC, and women with CD are at a higher risk for anemia.⁹

Anemia in IBD is mostly multifactorial, resulting, on the one hand, from chronic intestinal blood loss from inflamed intestinal mucosa combined with impaired iron absorption mainly as a consequence of inflammation but also in association with intake of proton pump inhibitors, persisting *H. pylori* infection or reduced food and thus impaired dietary iron uptake. Moreover, cytokines and acute phase proteins being induced upon inflammation impair iron availability for erythropoiesis; cause, a blunted biological activity of erythropoietin, and an inflammation driven impairment of erythroid progenitor cell proliferation.^{10,11} In general, anemia is found in various chronic inflammatory diseases, including cancer, infection, and autoimmune diseases, and this so-called anemia of chronic disease or anemia of inflammation is more prevalent in patients with advanced disease and those responding poorly to therapy.¹¹ Additionally, anemia in IBD patients occasionally may be

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OHN devised the study. OHN, MA, MC, and GW extracted, analyzed, and interpreted the data. wrote the first draft. All authors contributed to subsequent versions and approved the final version of the manuscript.

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induced or aggravated by drugs used for IBD treatment or by vitamin deficiencies, as well as rarely for various other reasons (eg, renal insufficiency, hemolysis, and innate hemoglobinopathies),¹² and a recent population based study revealed that patients with IBD have an insufficient intake of iron in their diet.¹³

Treatment of iron-deficiency anemia is very likely to have a beneficial impact on the affected patients because various organs may be disturbed as a result of the anemia [eg, central nervous system (impaired cognitive function, fatigue, “restless syndrome,” and depression), immune system (impaired reactive oxygen species production and alterations in cell functions), cardiorespiratory system (exertional dyspnea, tachycardia, palpitations, cardiac hypertrophy, systolic ejection murmur, and risk of cardiac failure), vascular system (hypothermia and pallor of skin), genital tract (loss of libido and menstrual problems), and gastrointestinal tract (anorexia, nausea, and motility disorders)].^{14,15}

The aims of this paper are to clarify the pathophysiology of anemia of IBD, to provide a balanced overview of the various forms of treatment, focusing on the approaches to iron replacement that are available for management, and to perform a systematic review to summarize the latest evidence (ie, within the last decade, during which intravenous regimens have been added to the therapeutic armamentarium) with respect to the diagnosis and treatment of choice for anemia in IBD. Finally, based on our systematic review, we aimed to provide an updated decision algorithm for the management of anemia in IBD.

PATHOPHYSIOLOGY OF ANEMIA IN INFLAMMATORY BOWEL DISEASE

Iron deficiency in IBD is caused by numerous factors, including increased iron loss from bleeding due to gastrointestinal inflammation and decreased iron absorption as a consequence of short bowel syndrome, loss of appetite during IBD flares, and inflammation-driven blockage of intestinal iron acquisition and macrophage iron reutilization.¹⁶ 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 (Hb), whereas the remainder is stored as ferritin, myoglobin, or within iron-containing enzymes. 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 by recycling iron from senescent erythrocytes.^{17,18} Total iron loss averages about 1–2 mg/day, mostly via the feces and cellular desquamation from the skin and intestine, as well as additional losses through menstruation.^{19,20}

Body iron homeostasis is regulated systemically by multiple mechanisms, among which the interaction of the liver-derived peptide hepcidin with the major cellular iron exporter ferroportin is of pivotal importance (Figure 1). The formation 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 iron deficiency, hypoxia, and anemia.^{21–23} Hepcidin targets ferroportin on the cell surface, resulting in ferroportin internalization and degradation and blockage of cellular iron egress.²² Whereas low circulating hepcidin levels enable an efficient transfer of iron from enterocytes and macrophages to the circulation in order to overcome iron deficiency, iron is retained in these cells when hepcidin levels are high and serum iron levels drop^{23,24} (Figure 1).

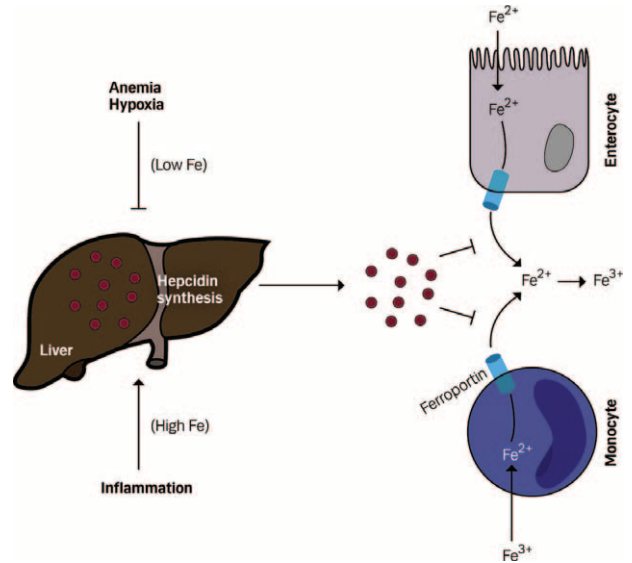


FIGURE 1. Regulation of systemic iron homeostasis by hepcidin. Enterocytes and monocytes release Fe^{2+} via the iron exporter ferroportin, which is then oxidized to Fe^{3+} and transported via the bloodstream. Liver-derived hepcidin inhibits iron efflux from these cells by binding to ferroportin, which promotes ferroportin internalization and degradation. The synthesis of hepcidin in the liver is induced by iron and inflammatory signals and suppressed by iron deficiency, anemia, or hypoxia.

Furthermore, inflammatory cytokines can directly inhibit iron absorption and stimulate the uptake and retention of iron in macrophages via hepcidin-independent pathways.²¹ Of interest, circulating hepcidin levels have an impact on the efficacy of oral iron therapy and can predict nonresponsiveness,²⁵ which is in line with experimental data demonstrating reduced intestinal ferroportin expression and iron absorption in individuals with increased hepcidin levels primarily as a consequence of inflammation.²⁴ 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. Cytokine-driven induction of hepcidin expression and the direct effects of cytokines on iron trafficking in macrophages play a decisive role in the development of this type of anemia (ie, anemia of chronic disease or the anemia of inflammation), by retaining iron in the reticuloendothelial system and blocking iron absorption, which results in an iron-limited erythropoiesis.^{11,26} The latter is reflected clinically by a reduced transferrin saturation that according to national guidelines is below 16% or 20%.²⁷ In addition, cytokines and chemokines further contribute to anemia by negatively affecting the activity of erythropoietin, by inhibiting the proliferation and differentiation of erythroid progenitor cells, and by reducing the circulatory half-life of erythrocytes.¹¹

Importantly, patients with active IBD suffer from chronic blood loss due to mucosal bleeding, which often causes true iron deficiency, as reflected by low ferritin levels.^{28,29} Moreover, true iron deficiency and anemia reduce hepcidin expression. These effects are transmitted by iron-deficiency-mediated inhibition of SMAD signaling in hepatocytes, anemia-induced and erythropoiesis-driven formation of hepcidin inhibitors such as erythropoietin and growth differentiation factor 15 (GDF-15),

and hypoxia-driven blockade of hepcidin formation via platelet-derived growth factor BB (PDGF-BB) or hypoxia-inducible factors (HIFs).^{30–34} Thus, in the presence of both inflammation and true iron deficiency due to bleeding in IBD, circulating hepcidin levels decrease because anemia and iron-deficiency regulatory signals dominate inflammation-driven hepcidin induction.^{34,35} Therefore, truly iron-deficient patients, even in the presence of systemic inflammation, are able to absorb considerable amounts of iron from the intestine.^{22,24}

Furthermore, vitamin deficiencies (eg, vitamin B₁₂, folic acid, and vitamin D) due to either intestinal inflammation or extensive bowel resection contribute to the development of anemia.^{29,36} Drugs used for the treatment of patients with IBD, such as proton pump inhibitors, sulfasalazine, methotrexate, and thiopurines, as well as functional impairment of the intestine due to inflammation or previous surgery, may aggravate anemia by negatively affecting iron absorption or erythropoiesis.³⁷

TREATMENT OF ANEMIA

The primary treatment of anemia of chronic disease is the cure of the underlying disease which in most cases leads to resolution or at least improvement of anemia unless other pathophysiological factors or deficiencies are involved.^{4,9,11,12,15} In cases of severe anemia (ie, Hb < 7–8 g/dL),^{38,39} specifically when it develops rapidly on the basis of acute gastrointestinal bleeding, or if the patient suffers from comorbidities resulting in aggravation of anemia-related symptoms such as coronary heart disease or chronic pulmonary disease, application of blood transfusions might be treatment of choice because this can rapidly

correct anemia and increase Hb levels.^{11,12,15,40} However, the indication for transfusions must be considered carefully as negative effects have been documented.^{40,41} These include an increased mortality in patients with liberal use of blood transfusions for the treatment of upper gastrointestinal bleeding,⁴² an increased nosocomial infection rate and mortality among intensive care patients,⁴³ higher frequency of surgical site infections,⁴⁴ the occurrence of transfusion-related anaphylactic reactions along with a small but residual risk for transmitting infections.^{45–47} Of note, if other easy-to-treat reasons contributing to anemia have been identified, such as vitamin deficiency, these should be corrected accordingly.

VARIOUS FORMS OF IRON REPLACEMENT

As imbalances of iron homeostasis are the major reason for anemia in IBD, this treatment strategy is in the focus of this review. Before going to the systematic analysis of clinical trials using oral and intravenous regimens, the currently available iron supplementation options are highlighted.

Oral Regimen

Oral iron supplementation is frequently used to treat iron-deficiency anemia partly because of an established safety profile, ease of administration, and a general low cost, although in a pharmacoeconomical setting the cost-effectiveness is more important.¹⁶ Oral iron supplements are available as either divalent Fe²⁺ (ferrous) salts or a trivalent Fe³⁺ (ferric) form coupled with sugar complexes.⁴⁸ The most widely used preparations are

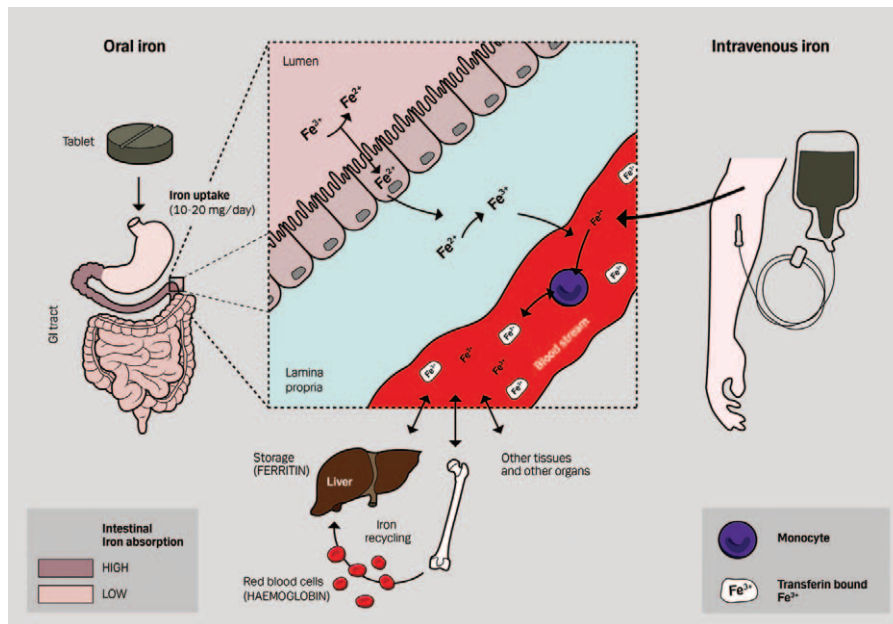


FIGURE 2. Iron absorption from oral or intravenous iron supplementation. Oral preparations of iron supplements are given as tablets and result in a daily absorption of 10–20 mg elemental iron (predominantly in the duodenum and upper jejunum). The oral iron supplementation mainly consists of the Fe²⁺ (ferrous) form that can be absorbed directly by enterocytes. Dietary iron, mostly in the Fe³⁺ (ferric) form, contains 10–30% of heme-bound iron, whereas the majority consists of nonheme iron (Fe³⁺ form). These 2 dietary iron formulations are taken up by enterocytes via different pathways with subsequent yield of Fe²⁺ which is exported to the circulation by ferroportin. Here, Fe²⁺ becomes oxidized to Fe³⁺ and specifically recognized and bound by transferrin and transported via bloodstream to target cells in the liver, bone marrow, and other tissues and organs for use or storage. Intravenous iron supplementation can be administered as high doses of iron directly in the bloodstream in its trivalent Fe³⁺ form, which is taken up by circulating monocytes (leading to an increase in their iron content), which redeliver Fe³⁺ to the blood circulation, where it is bound by plasma transferrin and transported to target cells.

ferrous sulfate, ferrous gluconate, and ferrous fumarate containing the ferrous form of iron because of the poor solubility of ferric-containing formulations. For absorption by enterocytes, Fe^{3+} needs to be reduced to Fe^{2+} (Figure 2), which is catalyzed by a membrane-bound ferric reductase and augmented by ascorbic acid.⁴⁹ Indeed, ascorbic acid (or vitamin C) facilitates increased absorption of oral iron.⁵⁰ However, a recent phase III study has reported that oral ferric maltol [a new compound under review by the European Medicines Agency (EMA)] is an efficient alternative treatment option for iron-deficiency anemia in IBD patients who are unresponsive to or intolerant of oral ferrous products.⁵¹

Although the optimal dose in IBD has not been established, the commonly recommended dose of oral iron for the treatment of iron deficiency is 50–200 mg/day of elemental iron once daily,⁵² but only a maximum of 10–20 mg/day of iron is absorbed in iron-deficient patients.^{49,53} Given that a high proportion of nonabsorbed ingested iron remains in the gut, oral iron supplementation is associated with gastrointestinal side effects such as nausea, vomiting, diarrhea, abdominal pain, and constipation in up to 20% of patients.^{3,16} Nausea and abdominal discomfort generally occur 1–2 hours after intake and tend to be dose related, although other gastrointestinal side effects such as constipation and diarrhea are idiosyncratic.^{52,53} Nonetheless, delayed-release enteric-coated iron tablets may be used in patients reporting such intolerances. However, these tablets may not be absorbed as effectively as standard preparations because they dissolve slowly in the duodenum, where most iron is absorbed (Figure 2).

Most of the anxiety regarding the use of oral iron therapy comes from studies in animal models of IBD that have provided contradictory evidence regarding exacerbation and/or improvement of inflammation.^{54,55} However, in humans, the evidence has been more controversial, and even though there is no convincing evidence that oral iron given in therapeutic dosages is effective in humans with active IBD,^{56,57} it is established that iron availability in the gut has a significant impact on the composition of the microbiome,⁵⁸ which has a central role in the pathogenesis of IBD.⁵⁹ The clinical significance of such changes remains speculative, but the evidence suggests that nutritional interventions may influence disease activity in patients with IBD.⁶⁰

Intravenous Regimen

Parenteral iron administration traditionally has been reserved for patients with intolerance or inadequate response to oral iron and for patients in whom a rapid increase in iron stores (replenishment) is desired (eg, patients scheduled for surgery in the short term).^{3,4,12} This approach is reflected in the indications approved by the US Food and Drug Administration (FDA) for a number of intravenous iron preparations,⁶¹ as well as the EMA.⁶² Although severe or life-threatening anaphylactic reactions upon intravenous iron administration occur very infrequently and have been mainly observed with high molecular weight dextrans in the past, the risk for such severe adverse reactions is much lower with currently used preparations, including high molecular weight iron components.⁶³ Compared with oral iron, intravenous iron seems to increase Hb and iron storage and improves quality of life more rapidly but not always more effectively.^{58,64} In addition, disadvantages include—apart from a generally higher cost—a risk of infusion-related adverse reactions, including anaphylaxis, which means that staff should be alerted to manage such potentially life-threatening situations.⁶³ Today, 6 intravenous iron preparations are available, including iron dextran, iron sucrose, and iron gluconate and, the more recently licensed compounds, ferric carboxymaltose, iron isomaltoside 1000, and ferumoxytol^{16,65,66} (Table 1). The structures of these new preparations are more stable and allow only a low level of labile iron to be released into the circulation, resulting in improved safety profiles.

Iron dextran exists in 2 stable forms: a low- (73 kDa) and a high-molecular-weight (165 kDa) complex, although the latter has been associated with an increased risk of anaphylaxis and anaphylactoid reactions.^{67–70} Thus, only low-molecular-weight iron dextran is currently available in Europe⁷¹ and can be given at a maximum single dose of 200 mg over a minimum of 30 min. Given the risk of anaphylactoid reactions, it was previously recommended to administer a test dose of iron dextran (ie, 0.5 mL at a gradual rate over 2–5 min) before giving a full dose, but the EMA no longer recommends this precaution.⁶²

Iron sucrose (43 kDa) and iron gluconate (37 kDa) are less stable and therefore can be administered in a maximal single dose of only 200 mg (300 mg in some countries) over a (minimum) infusion time of 30 minutes⁷² or 62.5 mg (in some countries 125 mg) over an infusion time of 5–10 min,⁷³ respectively, without a test dose.

TABLE 1. Characteristics of Different Intravenous Iron Preparations

Iron Preparation	Molecular Weight (kDa)	Carbohydrate Shell	Complex Stability	Maximum Approved Single Dose	Maximum total Dose
Iron dextran, low molecular weight	73	Dextran (branched polysaccharide)	High	200 mg (<30 min)	20 mg/kg
Iron sucrose	43	Sucrose (disaccharide)	Moderate	200 mg (≥30 min)	7 mg/kg (300 mg in some countries)
Iron gluconate	37	Gluconate (monosaccharide)	Low	62.5 mg (5–10 min)	62.5 mg (125 mg in some countries)
Ferric carboxymaltose	150	Carboxymaltose (branched polysaccharide)	High	1000 mg (≥15 min)	20 mg/kg
Iron isomaltoside 1000	150	Isomaltoside (linear oligosaccharide)	High	1000 mg (≥15 min)	20 mg/kg
Ferumoxytol*	721	Polyglucose sorbitol carboxymethylether	High	510 mg (≤1 min)	510 mg

* Not yet approved for IBD in Europe. The information given is from iron deficiency anemia in patients with chronic kidney disease.

However, higher dosages⁷⁴ or accelerated infusion rates⁷⁵ are associated with increased adverse events such as transient hypotension due to the release of labile iron. Thus, iron dextran, iron sucrose, and iron gluconate preparations typically require multiple administrations of lower doses to replenish iron stores.

The introduction of more advanced iron formulations, however, has permitted high-dose infusions (without test dosing) with minimal side effects because of the low levels of labile iron released during administration. Ferric carboxymaltose^{76–80} and iron isomaltoside 1000^{81,82} are highly stable 150-kDa complexes that are approved for clinical use. Their robust structures allow controlled and safe delivery of high-dose iron to the cells. Ferric carboxymaltose can be administered effectively and efficiently with a maximum single dose of 1000 mg over at least 15 minutes at a minimal interval of once per week.⁸¹ The structure of iron isomaltoside 1000 allows for administration of high single doses of up to 20 mg/kg of body weight within 15 minutes.⁸¹ Currently, there are limited data on iron isomaltoside 1000 in the treatment of iron-deficiency anemia in patients with IBD,⁸² although clinical trials are currently ongoing. Ferumoxytol is a much larger complex with a molecule weight of 721 kDa, which allows the drug to be given rapidly in relatively large doses. Although ferumoxytol is not yet approved for IBD in Europe, the current recommended intravenous dosing of this drug for patients with iron deficiency anemia due to chronic kidney disease is up to 510 mg in less than 1 min, with a second dose of 510 mg administered 3–8 days later.⁸³ Although limited data are available on ferumoxytol in the treatment of anemia in patients with various gastrointestinal diseases,⁸⁴ there are indications that the paramagnetic nature of ferumoxytol can interfere with MRI examinations.⁸⁵ Because MRI is an important diagnostic tool in the management of patients with IBD, this drawback may seriously hamper its use in this patient population. Further, in a recent analysis of different intravenous iron products in the United States, ferumoxytol had the highest rate for adverse events per million units sold of all products,⁸⁶ impeding its benefit–risk ratio, and since March 2015 it carries a boxed warning by FDA regarding potentially life-threatening allergic reactions.

Although different iron preparations have different side-effect profiles,⁶⁸ the most frequently reported complaints after infusion of large-molecule iron complexes are itching, dyspnea, wheezing, and myalgias. In this context, it should be noted that acute myalgia at the first administration of intravenous iron (without any other symptoms) that ablates spontaneously within minutes (ie, the so-called Fishbane reaction) does not recur at rechallenge.⁸⁷ Other, more certain side effects include hypotension, tachycardia, stridor, nausea, dyspepsia, diarrhea, and skin flushing, including periorbital edema. Serious side effects are rare⁸⁸ and include cardiac arrest,⁸⁹ but such problems are more common with older, mostly dextran-containing preparations.⁹⁰ Therefore, close monitoring for signs of hypersensitivity during and for at least 30 min after each administration of an intravenous iron formulation and reduction of the infusion speed on occurrence of discomfort are recommended.⁶²

SYSTEMATIC REVIEW OF CLINICAL TRIALS SINCE 2004 METHODS

Search Strategy

A systematic review was performed adhering to the guidelines established by the PRISMA Statement.⁹¹ A bibliographic search was performed in the PubMed and EMBASE databases

from January 2004 (ie, before the era of intravenous iron supplementation) to March 2015 using combinations of the following medical subject heading search terms: “inflammatory bowel disease” or “Crohn’s disease” or “ulcerative colitis” and “iron deficiency” or “anemia.” No prepublished protocol is accessible. Other sources of information were the Cochrane Library and the websites of WHO, FDA, and EMA. Figure 3 is a flowchart summarizing study identification and selection.

Selection Criteria

For the quality assessment, only original prospective studies evaluating the treatment of iron-deficiency anemia (ie, normalization of Hb concentration) in IBD patients with a minimum observation time of 4 weeks were included. Outcome assessment included correction of iron deficits causing anemia in IBD patients. Only English-language articles, excluding reviews and nonhuman investigations, were evaluated. Subsequently, articles were selected based on clinical relevance, and reference lists of relevant articles were hand searched to identify any additional studies.

Data Abstraction

Two authors (O.H.N. and M.C.) independently identified candidate articles from the results of the initial search on the basis of title and abstract. Subsequently, these 2 authors independently reviewed the full texts of candidate articles to identify interventions and assess study quality. Any discrepancies between the independent searchers were resolved in consensus with the 2 other authors (M.A. and G.W.).

Data Synthesis and Analysis

The literature search identified 13 randomized, controlled studies and prospective studies with and without control groups.^{51,54,64,69,72,77–80,84,92–94} Because of the considerable diversity in study designs (eg, oral and low- or high-dose intravenous drugs with different compositions), however, the authors were unable to conduct a meta-analysis.

The study was exempt from approval by the Scientific Ethics Committee of the Copenhagen Capital Region because the analysis involved only deidentified data, and all 13 studies included were granted individual ethics approval.

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RESULTS

The systematic search yielded a total of 632 studies, of which 13 prospective trials met the above-mentioned inclusion criteria (Figure 3) and included 2906 patients. Only data acquired from the systematic search are included in this section, and key data from each study are presented in Table 2 with results based on the conclusion of each individual study.

From the systematic review, it was revealed that apart from the WHO definitions of anemia³⁸ (ie, Hb level of <13 g/dL for men and <12 g/dL for women), transferrin saturation [TSAT; ie, the quotient of iron concentration (μmol/L) divided by transferrin concentration (mg/dL) in fasting blood samples multiplied with 70.9 stated as a percentage] of <20%, and serum ferritin concentration of <30 μg/L with a serum C-reactive protein (CRP) level within the normal range or a

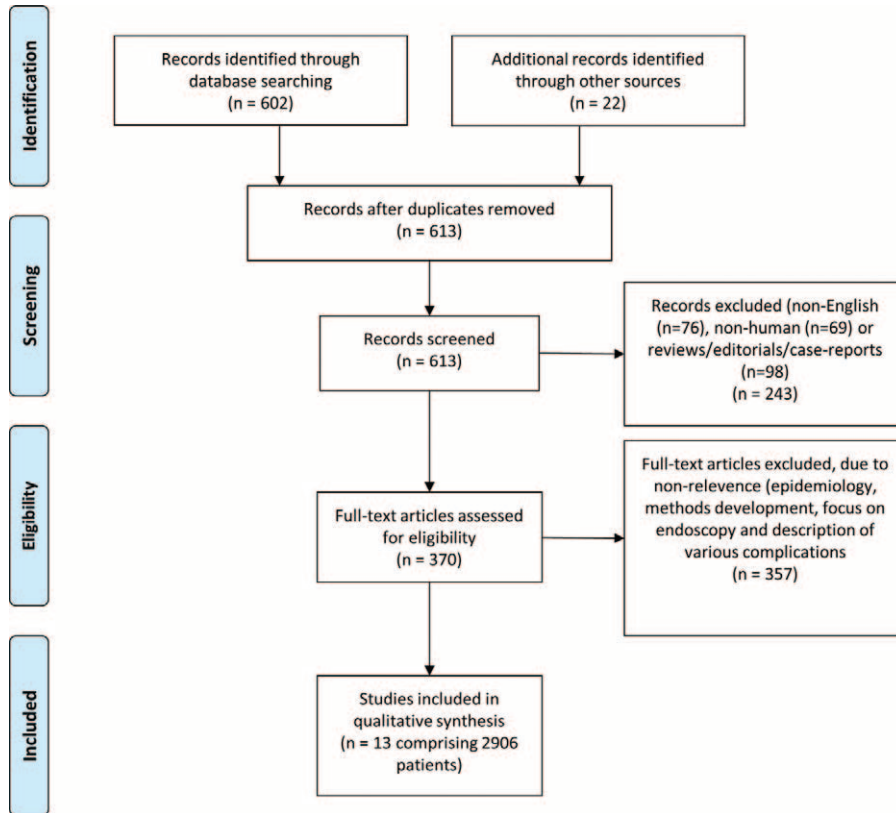


FIGURE 3. Flowchart of study screening process.

ferritin concentration of $<100 \mu\text{g/L}$ with an elevated serum CRP level comprised the laboratory tests used in the 13 studies for the diagnosis and assessment of iron-deficiency anemia in IBD.

Only 9 trials including oral iron supplementation in IBD patients have been published since 2004,^{51,54,64,69,72,79,80,92,94} but oral supplementation is from the published data well tolerated and has a positive effect on both Hb levels and body iron parameters (Table 2). From the studies included it seems that milder side effects (ie, abdominal discomfort, diarrhea, nausea, and vomiting) occurred less often after intravenous therapy as compared with oral therapy^{69,72,79,92,94} although 1 study did not report such differences.⁶⁴ From the studies included no comparison between side effects to various forms of oral supplementations was, however, performed. From an examination of the available data, it was apparent that there are no data indicating that oral iron supplementation exacerbates symptoms of the underlying IBD. Only 1 study in this systematic review reported worsening of disease activity in 2 of 33 patients with UC (but not in patients with CD).⁵⁴ However, in this study, the IBD quality-of-life scores improved significantly ($P = 0.016$) at the same time,⁵⁴ and when the 8 studies using oral iron supplementation were evaluated, it was apparent that an adequate level of evidence is provided to address the safety of oral iron supplementation in IBD. Of note, a very recent study with oral ferrous maltol suggests that this drug may be an alternative for patients who are unresponsive to or intolerant of formulations containing ferrous salts,⁵¹ which needs to be confirmed in future studies.

In the trials included in the systematic review, it was observed that administration of intravenous iron in IBD patients

frequently resulted in higher ferritin levels but not higher hemoglobin concentrations compared with oral iron supplementation in mild anemia ($\text{Hb} \geq 10 \text{ g/dL}$) and short-term follow-up,^{64,79,80,94} whereas in more aggravated iron deficiency anemia intravenous iron supplementation was superior to oral treatment regarding increase of Hb.^{69,80,92,94} Nevertheless, in all studies included in the systematic review, oral supplementation was administered for a minimum of 4 weeks with the target of normalizing Hb values.

In patients with IBD flares who have an inadequate response to experienced side effects with oral preparations, intravenous iron supplementation is the therapy of choice because it does not seem to exacerbate the clinical course of IBD and, in patients undergoing biological therapy with tumor necrosis factor (TNF) inhibitors, concomitant iron supplementation may be prescribed without affecting the disease course/activity.⁹³

Finally, it was established that the correction of anemia with iron supplementation is associated with a relevant improvement in the patient's quality of life.⁹²

DISCUSSION

For a long time, it was thought that the clinical symptoms of anemia occurred only when the Hb level dropped abruptly⁹⁵ and, conversely, that patients would adapt to low Hb levels if the anemia developed slowly. This led to the concept of *asymptomatic anemia*. In truth, the term *asymptomatic* seems to reflect the fact that impairments in physical condition, quality of life, cardiovascular performance, and cognitive function may be unrecognized by both patients and their physicians. Therefore, the process of adaptation in chronic anemia would seem to be

TABLE 2. Controlled Trials of Iron Deficiency Anemia Since 2004 Included in the Systematic Review

Authors	Route of Administration	Number of Patients, Disease Activity, and Follow-Up Time (wk)	Design, Inclusion Criteria, and End Point/Target	Findings
de Silva ⁵⁴	Oral ferrous sulfate (600 mg/day)	57 patients with IDA (22 with CD, 18 with UC (both groups quiescent to moderate disease activity), and 17 non-IBD) 4 weeks	Comparative study Hb < 13 g/dL, s-ferritin < 12 µg/L, hypochromic erythrocyte count >4% Target: normalization of Hb	Oral iron supplementation was rarely (6%) associated with increased disease activity of IBD. Four weeks of supplementation caused significant rises in Hb and iron stores (i.e., s-ferritin levels).
Schroder ⁷²	Oral (iron sulfate 100–200 mg/day for 6 weeks; n = 24) and low-dose intravenous sucrose (200 mg 1 to 2 times per week for 5 weeks; n = 22)	46 (29 CD, 17 UC) with quiescent and active disease (not specified) >5 weeks	Randomized either oral or intravenous Hb < 11.0 g/dL ♂ or 10.5 g/dL ♀, TSAT ≤ 20% or s-ferritin ≤ 20 µg/L Target: change in Hb	Equal short-term efficacy and safety of intravenous sucrose and oral iron supplementation for treatment of iron deficiency anemia in IBD (Hb, s-ferritin conc. and TSAT). Iron supplementation did not affect disease activity.
Katsanos ⁹³	Intravenous iron sucrose (dose 200–400 mg/infusion)	61 patients with “difficult to treat” IBD (eg, refractory disease in need of infliximab) with quiescent to severe disease activity 12 weeks (iron sucrose was interrupted at a transferrin saturation of >50%)	Open intravenous iron administered less than 12 weeks from last infliximab dose Hb < 12 g/dL, TSAT < 20% Target: Hb 12 g/dL	Infliximab and iron sucrose can be administered in combination with good tolerance, efficacy (Hb and TSAT), and overall safety. Iron supplementation did not affect disease activity.
Kulnigg ⁷⁹	Intravenous ferric carboxymaltose (1000 mg; n = 136) or oral ferrous sulfate (100 mg b.i.d.; n = 60)	196 patients (56 CD, 140 UC) with quiescent to severe disease activity 12 weeks	Randomized, open-label, comparative; endpoint was change in Hb from baseline to week 12 Hb ≤ 10 g/dL, TSAT < 20% or s-ferritin < 100 µg/L Target: change of Hb	Ferric carboxymaltose is not inferior to ferrous sulfate in terms of Hb, serum ferritin, and TSAT change over 12 weeks. Iron supplementation did not affect disease activity.
Gisbert ⁹²	Oral (525 mg ferrous sulfate; n = 78) and low-dose intravenous sucrose (200 mg twice a week; n = 22) based on Ganzoni’s formula	100 patients (59 CD, 41 UC) with quiescent and active disease (not specified) >12 weeks	Oral treatment at baseline for 3 months; insufficient response (ie, ≥1 g/dL) continued for extra 3 months; no response (ie, <1 g/dL): sucrose Hb < 13 g/dL ♂ or <12 g/dL ♀ plus at least 1 of the following: s-iron < 59 µg/dL, s-ferritin < 30 µg/L, TSAT < 12%, or s-transferrin > 400 mg/dL Target: normalization of Hb	Normalization of Hb concentration was found in the majority of IBD patients on oral treatment, whereas low-dose (sucrose) was an effective alternative in more severe anemia or intolerant patients. Iron supplementation did not affect disease activity.

Authors	Route of Administration	Number of Patients, Disease Activity, and Follow-Up Time (wk)	Design, Inclusion Criteria, and End Point/Target	Findings
Lindgren ⁹⁴	Oral (iron sulfate 800 mg/day, <i>n</i> = 46) and low-dose intravenous iron sucrose 200 mg every week or every second week; <i>n</i> = 45)	91 patients (44 CD, 47 UC) all in quiescent stage 20 weeks	Randomized, controlled, open-label study Hb \leq 11.5 g/dL, TSAT < 20% or s-ferritin < 30 μ g/L Target: increase of Hb	Intravenous iron sucrose treatment is superior to oral iron in correcting Hb, serum ferritin conc., and TSAT. Iron supplementation did not affect disease activity.
Evstatiev ⁷⁷	Intravenous high-dose ferric carboxymaltose (500–1000 mg/infusion, <i>n</i> = 244) versus low-dose iron sucrose (200 mg/infusion, <i>n</i> = 239)	475 patients with IDA (160 CD, 315 UC) in remission to moderate disease activity 12 weeks	Randomized, controlled, open-label study Hb < 13 g/dL ♂ or < 12 g/dL ♀, TSAT < 20%, s-ferritin < 100 μ g/L Target: Hb increase \geq 2 g/dL	A simplified fixed-dose ferric carboxymaltose regimen based on weight and baseline Hb is well tolerated and superior to the Ganzoni-calculated iron sucrose dosing regarding efficacy, compliance, and safety. Iron supplementation did not affect disease activity.
Khalil ⁶⁹	Oral (elemental iron) primarily ferrous sulfate (but also ferrous fumarate, polysaccharide–iron complex, sodium ferredetate, and ferrous gluconate, mean dose 103 mg/day) versus low-dose iron–dextrane (mean dose of 949 mg)	66 IBD patients who earlier had received iron supplementation (44 CD, 22 UC in remission or active disease not specified) received either oral or intravenous treatment (1:1) 8 weeks	Case-matched study in clinical practice Hb < 13 g/dL ♂ or < 12 g/dL ♀, TSAT < 16%, s-ferritin < 30 μ g/L with CRP in normal range and < 100 μ g/L with elevated CRP Target: increase of Hb	Oral iron should be used as first-line treatment, particular in mild anemia (\geq 10 g/dL) whereas intravenous iron treatment is suitable for those intolerant of or responding poorly to oral iron as evaluated from rise in Hb. Iron supplementation did not affect disease activity.
Evstatiev ⁷⁸	Intravenous high-dose ferric carboxymaltose (500 mg/infusion) versus placebo	245 nonanemic IBD patients who had previously completed the Evstatiev (2011) study (77) (76 CD, 169 UC in remission to moderate disease activity) 8 months [from completing Evstatiev (2011) study (77)]	Randomized, single-blind study to determine if administration of intravenous ferric carboxymaltose prevents recurrence of anemia in patients with IBD and low levels of serum ferritin previously treated for IBD-associated anemia within 8 months Hb < 13 g/dL ♂ or < 12 g/dL ♀ Target: time to recurrence of anemia	Serum ferritin–triggered iron therapy with ferric carboxymaltose is an effective and safe treatment to prevent recurrence of anemia evaluated by Hb and serum ferritin levels in patients with IBD who have responded to prior intravenous iron-replacement therapy. Iron supplementation did not affect disease activity.
Reinisch ⁶⁴	Intravenous iron isomaltoside (1000 mg; <i>n</i> = 219) or oral iron sulfate (200 mg daily; <i>n</i> = 108)	327 patients with IBD (103 CD, 224 UC in quiescent to mild disease activity) 8 weeks	Randomized, open-label, comparative; endpoint was compared by a noninferiority assessment with a margin of –0.5 g/dL Hb < 12 g/dL, TSAT < 20% Target: change of Hb	Noninferiority of intravenous iron isomaltoside versus oral iron was not demonstrated as assessed by Hb and TSAT. Iron supplementation did not affect disease activity.

Authors	Route of Administration	Number of Patients, Disease Activity, and Follow-Up Time (wk)	Design, Inclusion Criteria, and End Point/Target	Findings
Hetzel ⁸⁴	Intravenous ferumoxytol (510 mg; <i>n</i> = 406) or intravenous iron sucrose (200 mg; <i>n</i> = 199)	605 patients, of whom 138 had GI disorders incl. IBD (disease activity not specified) 5 weeks	Randomized, open label, nonblinded; endpoint: achieving ≤ 2 g/dL increase in Hb at week 5 compared with baseline Hb < 10 g/dL, TSAT < 20% Target: proportion of patents achieving > 2 g/dL increase of Hb	Ferumoxytol is as capable regarding safety and efficacy (Hb) as iron sucrose in IDA patients in whom oral iron is unsatisfactory or cannot be used. No differences of side effects between the two groups
Onken ⁸⁰	Intravenous ferric carboxymaltose (1500 mg; <i>n</i> = 246) or oral iron sulfate (975 mg daily; <i>n</i> = 253)	509 patients, of whom 53 had GI disorders incl. IBD (disease activity not specified) 5 weeks	Randomized, open-label, active-controlled among patients responding inadequately to oral iron for preceding 14 days (Hb increase < 1 g/dL) Target: highest observed Hb value from time of intervention and day 35. Hb < 11 g/dL, s-ferritin < 100 μ g/L	Ferric carboxymaltose is safe and superior to oral iron in increasing Hb and s-ferritin in IDA patients with inadequate oral iron response. Worsening of disease not reported.
Gasche ⁵¹	Oral ferric maltol (30 mg b.i.d.; <i>n</i> = 64) or placebo (<i>n</i> = 64).	128 IBD patients (70 CD, 58 UC) in remission or mild to moderate disease activity 12 weeks	Randomized, double-blind, placebo-controlled multicenter study among patients with iron deficiency anemia and documented failure of previous ferrous products Hb ≤ 9.5 –<12 g/dL for ♀ or – <13 g/dL for ♂ and s-ferritin <30 μ g/L at screening Target: change of Hb from screening to week 12	Ferric maltol provided clinically meaningful improvements in Hb and showed a favorable safety profile (the latter comparable to placebo). Iron supplementation did not affect disease activity.

the acceptance/toleration of an impaired quality of life.⁹⁵ Further, chronic fatigue caused by anemia may debilitate and even worry patients with IBD as much as abdominal pain or diarrhea.⁹⁵ Therefore, the beneficial effect on quality of life derived from the correction of anemia in patients with IBD may be as important to patients as the control of their abdominal symptoms.⁹⁵

To tailor the most appropriate therapy for iron deficiency and anemia in patients with IBD, some basic diagnostic analyses are mandatory^{21,27,56} (Table 3). Thus, during active inflammatory stages of IBD, laboratory measures of iron status are more difficult to interpret because inflammation affects the laboratory parameters of iron metabolism.⁹⁶ In the presence of chronic inflammation, the elevated transferrin levels characterizing iron deficiency may not be found because patients with low albumin levels tend to have lower transferrin concentrations.⁹⁷ Moreover, the serum ferritin level, the most accessible and well-known surrogate marker of stored iron,⁹⁸ can be normal or even increased in response to inflammation because ferritin expression is stimulated by several cytokines even in the

presence of true iron deficiency.⁹⁶ Therefore, although ferritin is generally considered to be the best indicator of iron deficiency, this parameter may not be reliable for the stored compartment in the setting of active inflammatory conditions, including IBD.^{11,96} Of note, both patients with inflammatory anemia and true iron-deficiency anemia have low transferrin saturation, which is a good indicator for a reduced availability of iron for erythropoiesis and thus has been used in a number of studies as a surrogate to determine the time to initiate iron therapy.^{53,56,95,99,100}

Comparative studies of intravenous versus oral iron supplementation in the systematic review did not demonstrate any significant difference in hemoglobin normalization favoring the use of intravenous iron therapy^{57,64,69,72,79,92} unless considered for patients with intolerance or an inadequate response to oral supplementation or during active disease stages. Moreover, a recent systematic review of randomized, controlled trials with the aim of assessing safety has demonstrated that intravenous iron therapy may increase the risk of infection.¹⁰¹

TABLE 3. Surrogate Markers of Importance for Assessing Anemia Due to Either Possible Coexisting Iron Deficiency (IDA), Chronic Disease (ACD), or Both (IDA + ACD)

Laboratory Test	Values Compared With Normal Range			Comments
	IDA	ACD	IDA + ACD	
Iron	Low	Low	Low	
Transferrin	High	Low to normal	Low	
Ferritin	Low	Normal to high	Normal to high	<30 ng/mL quiescent disease; >30 ng/mL active disease
TSAT	Low	Low	Low	<16–20%; observe circadian variation
sTfR/log ferritin	>2	<1	>2	
MCV/MHC	Low	Low to normal	Low to normal	
Reticulocyte Hb content (CHr)	Low	Normal	Low	
Vitamins (folate, B ₁₂ , D)	Normal	Low to normal	Low to normal	
Acute-phase proteins	Normal	Normal to high	Normal to high	
Hepcidin	Low*	High	Low to high	*Might be undetectable in true iron deficiency even in the presence of inflammation

CHr = reticulocyte hemoglobin content; MCV = erythrocyte mean cell volume; MHC = mean cell hemoglobin concentration; sTfR = soluble transferrin receptor; TSAT = transferrin saturation.

Because a great number of physicians are uncertain as to which diagnostic procedures and treatment regimen they should prescribe for their patients with iron-deficiency anemia,¹⁰² we performed an updated extensive review of the literature published in the last decade (during which novel approaches to intravenous iron supplementation have been introduced). In an independent screening and data extraction of references by 2 authors, only original prospective studies evaluating the treatment of iron-deficiency anemia in patients with IBD with a minimum observation time of 4 weeks were included, and the outcome assessment comprised correction of iron deficits causing anemia in patients with IBD. In terms of limitations, the studies included generally were characterized by small numbers of enrolled patients, were published solely in the English language, and were heterogeneous in design (ie, inclusion criteria and iron compositions administered, such as oral and low- or high-dose intravenous drugs), different enrollment populations as well as different lengths of therapy, and outcomes. Further, in some of the studies, a minimum 4-week treatment period was employed, although it is questionable whether such a short interval is always effective for the correction of iron deficiency in IBD, and thus the efficacy of the oral supplementation may be underestimated compared with a full treatment period of, for example, 3 months.

Based on our systematic review of the evidence, we developed an algorithm to help physicians in identifying IBD patients in need of iron supplementation and in selecting the most appropriate therapy regimen (Figure 4). If intravenous iron supplementation is considered, the use of older low-dose regimens is not recommended from the point of view of clinical practicality because a number of infusions might be needed over several days or weeks. Thus, high-dose regimens result in fewer infusions and increase the convenience and cost-effectiveness of intravenous iron repletion.

The optimal dosing strategy for intravenous compounds depends on the type of preparation and patient body weight and Hb concentration. The amount of iron needed to correct the Hb

concentration can be calculated using the Ganzoni equation,¹⁰³ although this formula might underestimate the iron needed when using a target Hb of 13 g/dL and iron stores of 500 mg.⁶⁴ Other, more simple schemes for the estimation of total iron need have been published.^{56,104} It should be mentioned that among patients with iron-deficiency anemia who are unresponsive even to intravenous iron supplementation (Hb increase ≤ 2 g/dL within 4 weeks), treatment with erythropoietin after ruling out other causes of anemia such as vitamin deficiencies, may be an option (Figure 4).^{105–107}

Finally, it should be highlighted that iron deficiency in IBD often relapses after iron replenishment.⁷⁸ Consequently, periodically monitoring, for example, every 3 months for a year and again after a year once the Hb value is normalized and iron stores are replenished to assess if retreatment is required.⁹⁸ However, we lack solid data 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.¹⁰⁸ Recent guidelines on the management of anemia in dialysis patients suggest that ferritin levels of up to 500 ng/mL appear to be safe. This limit also appears to be a useful upper a threshold in the management of patients with IBD and anemia.¹⁰⁹ Of note, in a recently published prospective single-center study, iron supplementation in chronic kidney disease patients was associated with a significant reduction in overall mortality.¹¹⁰ However, prospective studies will be necessary to clarify the impact of anemia correction and iron supplementation on the course of IBD and patient outcomes,¹⁰² as well as the definition of clinical endpoint, in order to optimize anemia management and iron supplementation in IBD patients.

CONCLUSIONS

The control of inflammation is a key objective in the treatment of IBD. Because iron-deficiency anemia has a considerable impact on patient quality of life, a thorough and

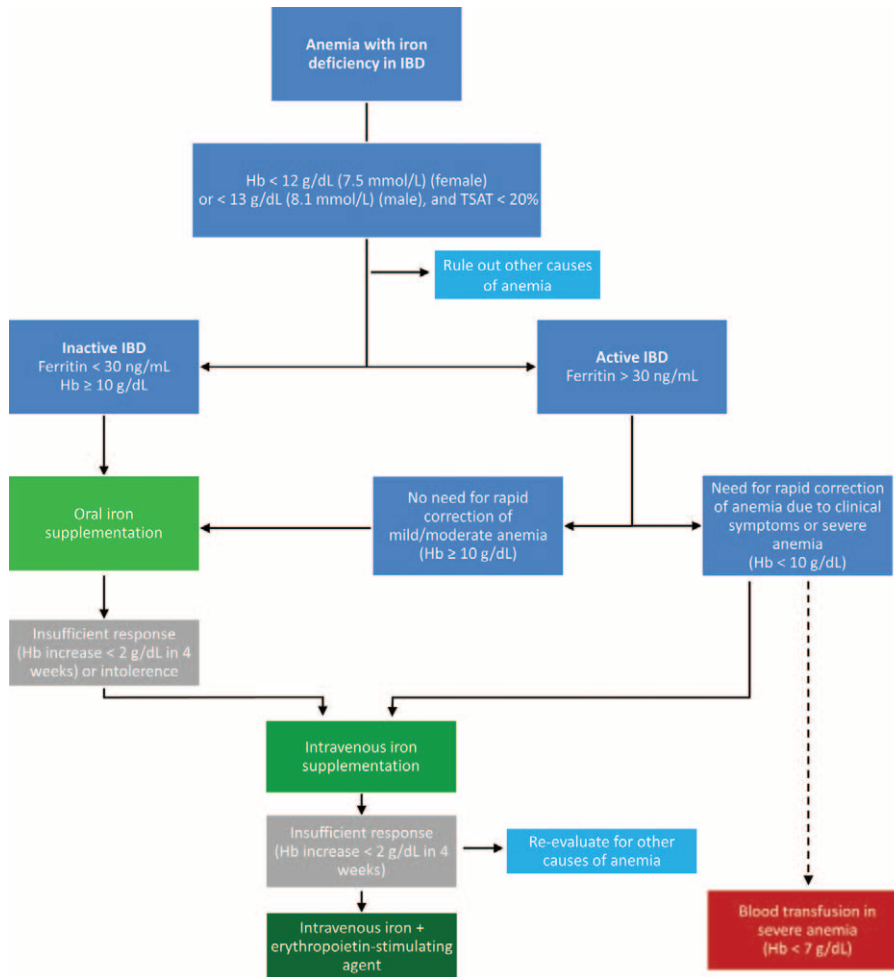


FIGURE 4. Algorithm for the treatment of anemia with iron deficiency in IBD. The decision tree provides a ready-to-use tool for clinicians to find the most appropriate therapy for patients with anemia/iron deficiency and IBD based on the data contained in this systematic review. Insufficient response is defined as a hemoglobin increase <2 g/dL within 4 weeks. Gastrointestinal intolerance to oral therapy is specified in the text. IBD = inflammatory bowel disease.

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 be uncertain concerning the optimal iron-replacement regimen should be prescribed. Based on the data presented herein, oral iron therapy should be preferred for patients with mild iron deficiency anemia (Hb ≥ 10 g/dL) in quiescent disease stages unless they are intolerant or have an inadequate response (Hb increase < 2 g/dL within 4 weeks),¹¹¹ whereas intravenous iron supplementation may be of advantage in patients with aggravated iron deficiency anemia or flaring IBD (Hb < 10 g/dL) because inflammation hampers intestinal iron absorption.^{10,112,113} In our systematic review, only 1 study showed oral iron supplementation to worsen disease activity in 2 patients with UC,⁵⁴ although quality of life improved significantly in the same group of patients, and intravenous iron supplementation seems to be safe in patients with active IBD. Finally, based on the available data, iron therapy can be administered concomitantly with TNF inhibitors,⁹³ a class of drugs used increasingly in the management of IBD.¹¹⁴

In summary, gastroenterologists treating patients with IBD need to pay attention to the management of anemia and iron deficiency for improvement in the general well-being of their patients a matter which frequently does not gain the attention it deserves. Here, we have presented an evidence-based algorithm for treatment of iron deficiency anemia in patients with IBD, but because of the high risk of anemia recurrence in this cohort, further clinical trials are warranted in an effort to optimize the treatment schedule in these patients.

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