

Diagnosis and treatment of anemia in patients with inflammatory bowel disease

Victoria Mücke^{a*}, Marcus M. Mücke^{a*}, Tim Raine^{b**}, Dominik Bettenworth^{c**}

J. W. Goethe University Hospital, Frankfurt, Germany; Addenbrooke's Hospital, University of Cambridge, Cambridge, UK; University Hospital Münster, Münster, Germany

Abstract

Anemia represents one of the most frequent complications in inflammatory bowel disease (IBD) and severely impairs the quality of life of affected patients. The etiology of anemia in IBD patients can be multifactorial, often involving a combination of iron deficiency (ID) and anemia of chronic disease (ACD). Although current guidelines recommend screening for and treatment of anemia in IBD patients, current observational data suggest that it still remains underdiagnosed and undertreated. Besides basic laboratory parameters (e.g. mean corpuscular volume, reticulocyte count, serum ferritin, transferrin saturation, etc.), the concentration of soluble transferrin receptor (sTfR) and novel parameters such as the sTfR/log ferritin index can guide the challenging task of differentiating between ID and ACD. Once identified, causes of anemia should be treated accordingly. This review summarizes our current understanding of anemia in IBD patients, including the underlying pathology, diagnostic approaches and appropriate anemia treatment regimens.

Keywords Inflammatory bowel disease, anemia, iron deficiency

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Introduction

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), represents a spectrum of chronic, remitting disorders of the gastrointestinal tract of unknown etiology [1,2]. Besides symptoms primarily resulting from intestinal inflammation, IBD patients can develop various extra-intestinal manifestations [3]. Anemia appears to be one of the most frequent complications of IBD [4,5]. Reported prevalence rates are highly variable and may approach up to 74% [4,6]. Heterogeneity in reported

rates in part reflects poorly standardized definitions of anemia. Although the World Health Organization (WHO) anemia criteria [7] are widely accepted (Table 1), they have been questioned on the basis of differences in ethnicity or local environment [8,9]. Additionally, in a recent survey across European countries, Stein *et al* revealed that differences between patient cohorts may contribute to diverging data. For example, whilst reported prevalence rates amongst outpatients range up to 16%, similar data for hospitalized patients exceed 65% [10,11]. A recent meta-analysis of individual patient data from 2192 European patients determined the overall prevalence of anemia in IBD patients to be 24%, with a reported occurrence of severe anemia in 2.75% of patients analyzed. In the same study, the overall prevalence was higher in CD than in UC patients [12].

Unfortunately, over the past decades anemia in IBD has received little attention [13], reflected perhaps in only marginal coverage in former international guidelines for the management of IBD [14]. In contrast, in recent years the topic has moved into the spotlight, because there is a growing body of evidence that anemia plays a key role in affecting IBD patients' quality of life (QOL). In 2014, Danese *et al* analyzed anemia-related symptoms from an IBD patient's perspective [15]. Symptoms widely reported by the 613 participants included fatigue, weakness, difficulties in concentrating, depressive mood, breathlessness, and sleeping difficulties. Patients affected by fatigue reported a major negative impact on daily life, including physical activities, productivity and home life (76%, 63% and 60%, respectively). Several other studies have confirmed that

Departments of ^aInternal Medicine 1, J.W. Goethe University Hospital, Frankfurt, Germany (Victoria Mücke, Marcus M. Mücke); ^bMedicine, Addenbrooke's Hospital, University of Cambridge, Cambridge, UK (Tim Raine); ^cMedicine B, University Hospital Münster, Münster, Germany (Dominik Bettenworth)

*Victoria Mücke and Marcus M. Mücke share equal first authorship

**Tim Raine and Dominik Bettenworth share equal senior authorship

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Correspondence to: Dominik Bettenworth, MD, Department of Medicine B, University Hospital Münster, Albert-Schweitzer-Campus 1, D-48149 Münster, Germany, Tel.: +49 251 834 7661, Fax: +49 251 834 7570, e-mail: dominik.bettenworth@ukmuenster.de

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anemia in IBD further worsens an already impaired QOL, while its treatment significantly increases QOL [16-18].

Although current guidelines recommend the treatment of anemia in IBD patients, recent evidence suggests that anemia remains underdiagnosed and undertreated. For example, Blumenstein *et al* revealed that in Germany 56.5% of IBD patients with anemia had not received adequate treatment [19]. Likewise, a web-based questionnaire of IBD patients showed that one third of those with anemia had not been treated accordingly [15]. Additionally, in a recent survey across 9 European countries, Stein *et al* revealed a high frequency of iron deficiency (ID) among IBD patients [20]. Moreover, the authors of the latter study observed that gastroenterologists, in clinical practice, frequently deviate from international guidelines concerning iron supplementation in IBD patients.

Pathophysiology of anemia in IBD

In IBD patients, anemia represents a systemic complication or extra-intestinal manifestation that can be multifactorial

Table 1 Minimum hemoglobin and hematocrit levels used to define anemia in people living at sea level [WHO, UNICEF, UNO. Iron deficiency anemia: assessment, prevention and control. Report of a joint WHO/UNICEF/UNU consultation. Geneva: World Health Organization; 1998]

Age or sex group	Hemoglobin (g/dL)	Hemoglobin (mmol/dL)	Hematocrit (%)
Children ½ to 5 years	11.0	6.83	33
Children 5 to 11 years	11.5	7.14	34
Children 12 to 13 years	12.0	7.45	36
Non-pregnant women	12.0	7.45	36
Pregnant women	11.0	6.83	33
Men	13.0	8.07	39

in origin (Fig. 1), but is typically caused by a combination of ID and anemia of chronic disease (ACD) [21]. It is well known that a significant number of IBD patients develop ID. A combination of chronic intestinal blood loss, dietary restrictions and/or iron malabsorption caused by mucosal inflammation or surgical bowel resections (especially in CD patients) leads to a disequilibrium of iron demand and absorption [4,11,22].

Iron is an essential mineral that is mostly bound in hemoglobin (Hb). After ingestion, dietary iron is reduced from its ferric (Fe^{3+}) to its ferrous (Fe^{2+}) form and absorbed predominantly in the duodenum at the apical surface of enterocytes through the divalent metal transporter. Although dietary iron is poorly absorbed, a major additional source of iron in the diet comes from that bound to animal heme, which is taken up into cells by a poorly understood mechanism and degraded to release bound iron. Subsequently, iron undergoes transfer through the basolateral membrane via the dedicated ferroportin channel, before oxidation back to Fe^{3+} . In the circulation, elemental iron is almost entirely bound by transferrin and distributed throughout the body [11,23]. Iron absorption is crucially regulated by the peptide hepcidin which is principally produced in the liver [24]. It reduces iron absorption in cases of iron overload or upon induction by proinflammatory cytokines, including interleukin (IL) -6 and bone morphogenetic protein [25,26]. Notably, these proinflammatory cytokines are elevated in active IBD, while hepcidin levels can be further increased by malignancies, autoimmune diseases (e.g. rheumatoid arthritis) or chronic kidney diseases [27-29]. Elevated levels of hepcidin then result in internalization and degradation of ferroportin, leading to impaired iron absorption [30] as well as to iron retention in macrophages and monocytes [31]. Recently, several studies confirmed increased serum levels of hepcidin in IBD patients. For example, Basseri *et al* observed a strong correlation between hepcidin expression and proinflammatory IL-6 levels in patients with CD [32]. In line with this observation, Semrin *et al* demonstrated that intestinal iron absorption was

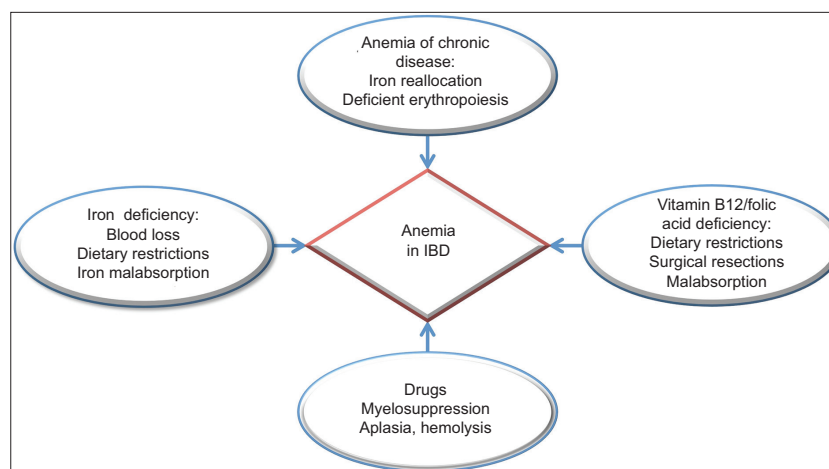


Figure 1 Predominant causes of anemia in inflammatory bowel disease (IBD). While iron-deficiency anemia of chronic diseases and mixed forms are the most common causes for anemia in IBD patients, lack of vitamin B12 as well as folic acid and IBD-related medication can also contribute to anemia development

decreased in CD patients with active disease compared to CD patients in remission [33].

ACD represents the second major cause of anemia in IBD. Although its pathophysiology remains complex, three core mechanisms have been identified which jointly culminate in ACD: 1) iron redistribution out of the serum due to increased hepcidin levels, including retention in macrophages and monocytes (blurring the differentiation between ID and ACD, see above); 2) deficient maturation and proliferation of erythroid progenitor cells; and 3) a reduced erythrocyte lifespan [34]. Additionally, several cytokines that are overexpressed in chronic diseases, such as tumor necrosis factor (TNF)- α , IL-1 or interferon (IFN)- γ , further contribute to this process. In 1987, Roodmann *et al* were the first to report that TNF- α inhibits erythropoiesis [35]. It is now known that TNF- α not only directly inhibits erythropoiesis [36], but also indirectly impairs this process by downregulation of erythropoietin [37,38]. Likewise, hepcidin and IL-1 are also capable of reducing the concentration of erythropoietin [38,39]. Additionally, IFN- γ further drives the development of anemia by inhibiting erythroid colony growth [40], shortening the lifespan of erythrocytes via increased turnover in the spleen [41], and increasing apoptosis mediated by TNF-related apoptosis-inducing ligand or TNF-like weak inducer of apoptosis in erythroid progenitor cells [42,43].

Aside from ID and ACD, anemia in IBD patients can result from impaired vitamin B12 and folic acid absorption. Vitamin B12 and folic acid deficiency is found in up to 33% and 29%, respectively, of patients with CD [44-47]. Reasons include dietary restrictions, as well as impairment of ileal absorption (typically through a combination of ileal inflammation, bacterial overgrowth and/or surgical resection, leading to reduced vitamin B12 and folic acid absorption) [45,46]. In UC, vitamin B12 and folic acid deficiency is less common but can occur in up to 16% and 8.6%, respectively [44-47]. Possible causes include ileal dysfunction following proctocolectomy and ileal pouch-anal anastomosis, bacterial overgrowth and reduced intestinal transit time [44,48].

Finally, anemia can also occur as a side effect of IBD therapeutics. While toxicity of thiopurines towards the bone marrow is widely recognized and appears in approximately 3% of cases per patient/year of treatment [49,50], anemia has also been found to be related to sulfasalazine therapy through reduced folate absorption and aplasia or hemolysis, although this is rarely reported [51,52].

Diagnosis of anemia in IBD patients

In humans, multiple factors, such as age, sex, ethnicity, pregnancy, environment and nutrition, influence Hb levels [53,54]. In general, the WHO defines anemia as a decline in blood Hb according to the reference levels given in Table 1. These cutoff levels apply equally to IBD patients, as the definitions do not vary according to comorbidities. Considering the high prevalence of anemia in chronic inflammatory diseases, the recently published European Crohn's and Colitis Organization (ECCO) guideline on

anemia recommends regular screening, according to disease severity and activity [21]. More specifically, anemia assessment in outpatients with active inflammation (high elevated inflammatory biomarkers or significant endoscopic proof of disease activity) should be performed at least every three months, whereas screening intervals in outpatients who show few signs of systemic inflammation or are in remission can be extended to every six to twelve months. Special attention should be paid to children and adolescents [55]. Common diagnostic markers for anemia assessment may be applied to patients without clinical, endoscopic or biochemical evidence of active disease. In contrast, in IBD patients who have active disease, are receiving ongoing therapy, or have undergone extensive small bowel resection, important parameters for the assessment of anemia, such as erythrocyte indices, ferritin and transferrin saturation (TfS), do not always afford sufficient accuracy. It should be remembered that ferritin is an acute-phase protein that is increased in the context of ongoing systemic inflammation [56]. Furthermore, differentiation between the two most frequent types of anemia in IBD patients, ID and ACD, remains challenging, especially since both conditions frequently coexist.

Traditionally, the distinction between different causes of anemia is based on a hematological algorithm starting with the interpretation of the mean corpuscular volume (MCV). Accordingly, micro-, macro- or normocytic erythrocyte conditions may hint at different causes for anemia. Besides MCV, basic laboratory parameters should include reticulocyte count, differential blood cell count, red cell distribution width, and serum ferritin, TfS and C-reactive protein (CRP) concentrations [21]. In patients with postoperative CD or severe ileitis, serum levels of vitamin B12 and folic acid should also be evaluated. In patients with signs of hemolysis or significant comorbidities, haptoglobin, the percentage of hypochromic red cells, reticulocyte Hb, lactate dehydrogenase, soluble transferrin receptor (sTfR), creatinine, and urea should be determined accordingly [21]. Some authors have also emphasized a key potential role for early markers of impaired erythropoiesis markers, such as the Hb content in reticulocytes (CHr) or reticulocyte Hb equivalent, measures that are not available as part of conventional laboratory tests and that are further discussed in the outlook section [57].

ID anemia in IBD patients

Low serum ferritin levels (<30 $\mu\text{g/L}$), high transferrin levels and a decreased MCV index are routinely used to screen for ID [58]. In IBD-patients, these parameters may not always allow for reliable conclusions, because of overlapping causes of anemia and multiple confounding factors (see above). In particular, active inflammation can result in falsely normal or elevated ferritin levels as part of an acute-phase reaction [5]. Under chronic inflammatory conditions, other parameters of low iron stores are also less interpretable, as a result of changes such as increased platelet counts [59] or low transferrin levels [60]. In these cases, it is important to consider that serum ferritin levels up to 100 $\mu\text{g/L}$ do not adequately exclude

ID [61]. Therefore, the concentration of sTfR may indicate the status of iron supply more precisely, since this parameter is not influenced by chronic inflammation [62]. Recently, the ratio of sTfR to the logarithm of serum ferritin (sTfR/log ferritin index) has been reported as providing more accuracy in differentiating ID anemia from ACD [63,64]. For example, a prospective multicenter observational trial in a cohort of 145 non-IBD patients with anemia demonstrated the utility of the sTfR/log ferritin index [65]. Skikne *et al* demonstrated that subjects with ID anemia or ACD + ID anemia had significantly higher sTfR and sTfR/log ferritin index values than subjects with ACD. ROC curves produced cutoffs of 21 nmol/L for sTfR and 14 (using nmol/L) for the sTfR/log ferritin index. The sTfR/log ferritin index was superior to sTfR.

ACD in IBD patients

Functional ID is a state in which there is insufficient iron incorporation during erythropoiesis, despite normal total body iron stores, and it is a major component of ACD. Therefore, besides “true” ID anemia, functional ID should be considered if serum ferritin is >100 µg/L and TfS below 20% [21]. Again, sTfR/log ferritin may help discriminate absolute from functional ID anemia [34,66]. In patients with evidence of inflammation and intermediate serum ferritin levels (<100 µg/L but >30 µg/L), a value of sTfR/log ferritin >2 may indicate a combined anemic status, whereas a ratio <2 is consistent with normal total body iron stores [34].

Non-ID anemia in IBD patients

As described above, there are several additional important causes of Hb deprivation in patients with IBD. Especially in cases of macrocytic anemia, vitamin B12 and folic acid level measurements should be performed during screening visits [44]. Additionally, myelosuppressive medication, including thiopurines and sulfasalazine, should always be considered in the diagnostic workup of anemia [49,52].

Treatment of anemia in IBD

Given that anemia significantly affects patients' QOL and increases disease severity and mortality rates, therapeutic interventions aiming to normalize Hb levels play a crucial part in the clinical management of IBD patients [61]. Physicians should be aware of anemia in IBD patients and should treat the underlying causes.

Iron therapy in IBD

Recent guidelines strongly recommend iron supplementation in patients with confirmed ID anemia [11,67,68]. The

normalization of Hb levels and repletion of iron stores are considered as final therapeutic goals. More specifically, a Hb increase of >2 g/dL and a transferrin saturation of >30% within 4 weeks are regarded as adequate therapeutic responses [11,69]. Iron supplementation in IBD patients without manifest anemia is still debated and should be further evaluated in clinical trials, especially with regard to tolerance of therapy.

Normal diets usually provide sufficient iron supplies in the form of elemental and heme iron. As already discussed, in patients with active IBD, the inflammation of the mucosa leads to maldigestion, malabsorption and changing nutrition habits [33,70,71], which may aggravate ID and make exclusive nutritional supplementation impossible. Nevertheless, oral iron substitution can be effective in IBD patients with mild disease activity and mild anemia [72,73]. For reasons of widespread availability, low cost and established safety profile, many physicians tend to favor oral iron substitution as first-line therapy. Frequently used oral iron supplements are ferrous fumarate (325 mg tablets containing 106 mg elemental iron per tablet), ferrous sulfate (325 mg tablets containing 65 mg elemental iron per tablet), and ferrous gluconate (325 mg tablets containing 36 mg elemental iron per tablet).

However, in the light of several reports of adverse events [74] and additional mucosal harm [72] in IBD patients during oral iron replacement therapy, oral supplementation must be evaluated in terms of effectiveness and tolerability [75-77]. Animal trials indicate that oral and rectal iron intake can lead to an aggravation of disease activity through the increased production of proinflammatory cytokines, such as IL-1, IL-6, TNF- α and IFN- γ [78]. This may be linked to increased flux in the classic Fe²⁺-catalyzed Fenton reaction that triggers the production of reactive oxygen species by neutrophils in the mucosa [79].

For these reasons, intravenous iron supplementation is currently still favored in IBD patients with ID anemia, especially in cases of severe anemia (Hb <10 g/L), or inadequate response to or intolerance of oral supplementations [80,81], not least because it is well-tolerated by most patients [15]. Furthermore, intravenously administered iron does not deteriorate disease activity in IBD patients [80,82]. In early trials, modern preparations of ferric iron, such as Monofer® (iron isomaltoside) and Ferinject® (ferric carboxymaltose) were well tolerated in terms of the acute toxicity profile, efficacy and tolerance in IBD patients. In general, newer non-dextran intravenous formulations seem to be superior to preparations containing elemental iron complexed with dextrans, especially in terms of reduced rates of anaphylactoid reactions. In practice, this means that non-dextran formulations can be given at a faster rate and are not complicated by the requirement for the application of a test dose [73,83-85].

Previously, the Ganzoni formula has been widely used to estimate iron requirements and dosage, although this has been criticized as inconvenient, inconsistent and inaccurate [21]. More recently, a novel scheme of total iron calculation has been proposed and provides a simple and efficient dosing regimen (Table 2, [84]). Although this scheme has only been evaluated for the dosing of intravenous ferric carboxymaltose, physicians have broadly adopted it for use with other intravenous iron

Table 2 Estimated total iron need in inflammatory bowel disease patients with iron-deficiency anemia [75]

Hemoglobin g/dL	Body weight <70 kg	Body weight ≥70 kg
10-12 (women)	1000 mg	1500 mg
10-13 (men)	1000 mg	1500 mg
7-10	1500 mg	2000 mg

products. Adjustments may be made in patients with very severe anemia (<7.0 g/dL). In these patients, experts suggest an additional dosage of 500-1000 mg according to evaluated tolerability [86].

After successful initial treatment of ID anemia, IBD patients are still at an increased risk of anemia recurrence and may benefit from prophylactic iron substitution [87]. Again, initial infusions with ferric carboxymaltose (Ferinject®) seem to adequately prevent recurrences [88]. Recent data suggest an intravenous iron re-treatment as soon as serum ferritin drops below 100 µg/L or recurrence of anemia occurs [84]. Notably, however, Ali *et al* demonstrated that up to 8 weeks after intravenous iron-dextran therapy, ferritin levels may not sufficiently reflect the availability of iron in patients' bone marrow [89], suggesting that clinicians should avoid assessing the response too soon after therapy.

Therapy of ACD in IBD

After diagnosing ACD and addressing any coincident ID, treatment of ACD should focus on optimization of IBD treatment to control disease activity. In addition, concurrent infections, inflammation or malignancies should also be considered and addressed when identified [21]. Furthermore, erythropoietin-stimulating agents in combination with intravenous iron supplementation may additionally be administered with beneficial effects in ACD anemia [5,90,91]. In some studies, erythropoietin has also already been shown to attenuate intestinal inflammation and to promote epithelial tissue regeneration [92]. Additionally, TNF-α-induced bone marrow suppression may require the use of anti-TNF therapy to support bone marrow output [93].

Treatment of trace element and vitamin deficiency anemia

In patients with active IBD, or especially after ileal resection, signs of mixed anemia or high MCV levels should be seen as an indication for the measurement and direct supplementation of vitamin B12 and folic acid [21].

Outlook

As mentioned above, the sTfR/log ferritin index is seen as a promising biomarker of iron availability and has been

integrated into new diagnostic algorithms to differentiate ID anemia from ACD [63,65]. Furthermore, Enko *et al* discussed the accuracy of the combined evaluation of the iron-transporter binding protein hepcidin-25, along with ferritin [94] and proposed hepcidin-25 quantification, to assess functional ID, particularly in patients with elevated serum CRP levels >5 mg/L [95].

Furthermore, characterization of the reticulocyte function by using novel indices such as CHR can allow rapid detection of ID and additionally provides a measure of recent bone marrow output. This may be of particular value under situations of rapid changes (e.g. assessing response to recent iron therapy), since conventional erythrocyte indices will be affected by the comparatively long lifespans of mature erythrocytes, which extend up to 120 days [96]. Moreover, Urrechaga *et al* described a method for the early detection of coincident ID in patients with established ACD through measuring the percentage of hypochromic erythrocytes (%Hypo-He), reporting that the technique showed promising reliability. This parameter visualizes the portion of mature erythrocyte red cells with inadequate Hb loading and is said to increase earlier than common ID biomarkers [97]. Importantly, both CHR and %Hypo-He are likely to be in the normal range in uncomplicated and non-overlapping ACD [96,97]. Nevertheless, clinical trials in IBD patients are needed to confirm the reliability, validity and necessity of the all above-mentioned potential new biomarkers.

Novel preparations have been designed to address intolerance to oral iron supplementation. For example, ferric maltol has been shown to provide satisfactory efficiency in mild to moderate anemia in IBD and good tolerability rates, even in patients who have previously been intolerant to other oral supplementation drugs [98]. Reaching the intestinal mucosa as a stable complex, ferric iron with maltol seems to allow a more efficient iron uptake than ferrous iron salts [99,100].

Other novel treatment options for ACD in IBD focus on hepcidin antagonism. Preliminary results from preclinical studies in monkeys show promising effects on specific iron mobilization [101,102], but need to be further evaluated in clinical trials in human patients.

Concluding remarks

ID anemia is frequently observed in IBD patients. Thus, all IBD patients should be screened on a regular basis (in accordance with disease severity) for ID and ID anemia. Complete blood count, serum ferritin and CRP value constitute an appropriate screening standard, while the detection of decreased Hb values warrants a more extended diagnostic anemia workup. In IBD patients with ID anemia, iron substitution remains indispensable and the advantages as well as the disadvantages of oral and intravenous formulations should be considered carefully.

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