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Inflammatory Bowel Disease (G Lichtenstein, Section Editor)

Management of Anemia in Patients with Inflammatory Bowel Disease (IBD)

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Abstract

Purpose of Review Anemia is the most common complication as well as an extra intestinal manifestation of inflammatory bowel disease (IBD). It is associated with a significant impact on patient's quality of life (QoL); as well it represents a common cause of frequent hospitalization, delay of hospital inpatient discharge and overall increased healthcare burden. In spite of all these, anemia is still often underdiagnosed and undertreated. Our aim in this review is to provide a pathway for physicians to help them achieve early diagnosis as well as timely and appropriate treatment of anemia which in turn would hopefully reduce the prevalence and subsequent complications of this condition among IBD patients.
Recent Findings The etiology of anemia among IBD patients is most commonly due to iron deficiency anemia (IDA) followed by anemia of chronic disease. Despite this, more than a third of anemic ulcerative colitis (UC) patients are not tested for IDA and among those tested and diagnosed with IDA, a quarter are not treated with iron replacement therapy. A new algorithm has been validated to predict who will develop moderate to severe anemia at the time of UC diagnosis. While oral iron is effective for the treatment of mild iron deficiency-related anemia, the absorption of iron is influenced by chronic inflammatory states as a consequence of the presence of elevated levels of hepcidin. Also, it is important to recognize that ferritin is elevated in chronic inflammatory states and among patients with active IBD, ferritin levels less than 100 are considered to be diagnostic of iron deficiency. Newer formulations of intra-venous (IV) iron have a good safety profile and can be used for replenishment of iron stores and prevention of iron deficiency in the future.

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Summary Routine screening for anemia is important among patients with IBD. The cornerstone for the accurate management of anemia in IBD patients lies in accurately diagnosing the type of anemia. All IBD patients with IDA should be considered appropriate for therapy with iron supplementation whereas IV administration of iron is recommended in patients with clinically active IBD, or for patients who are previously intolerant to oral iron, with hemoglobin levels below 10 g/dL, and in patients who need erythropoiesis-stimulating agents (ESAs). As the recurrence of anemia is common after resolution, the monitoring for recurrent anemia is equally important during the course of therapy.

Introduction

Inflammatory bowel disease (IBD), which comprises ulcerative colitis (UC) and Crohn's disease (CD), represent chronic inflammatory conditions involving gastrointestinal tract with a variable clinical course. However, in addition to the intestinal involvement, IBD can have a variety of extra intestinal manifestations whose severity may be dependent or independent of the clinical course of IBD. These may be organ specific with the involvement of joints, eyes and skin or systemic manifestations including malnutrition and anemia [1, 2].

Anemia is the most common complication and extra intestinal manifestation of IBD [1, 3, 4]. Previous studies on this subject have shown that the prevalence of anemia ranges from 6 to 74% in hospitalized IBD patients [5–8]. Population-based datasets found that the prevalence of anemia was 19–21% among outpatients IBD patients [9, 10]. A systemic review by Filmann et al. comprising nine European countries showed that the overall prevalence of anemia in patients with CD was 27%, whereas in UC patients it was 21% [11•]. Also, the prevalence of anemia was more common in CD as compared to UC patients [12, 13]. In addition, a recent study of a Swedish cohort highlighted that the prevalence of anemia was significantly higher in hospitalized CD and UC patients compared to the outpatient population [12].

The most common cause of anemia in patients with IBD is iron deficiency anemia (IDA) followed by anemia of chronic disease (ACD) [14, 15]. Other less frequent causes of anemia in IBD include vitamin B12 deficiency and folate deficiency as well as medication-induced anemia among others etiologies. Anemia has a significant impact on the disease and is associated with reduced quality of life (QoL), such as physical, emotional and cognitive function [16, 17]. It is also a common cause of frequent hospitalization, delay of discharge and increased health-care burden [18]. Interestingly, it has been shown that the correction of anemia in IBD patients improves their health-related QoL and overall patient well-being and this improvement is independent of clinical activity of disease [17, 19, 20].

Despite being a common disease-related complication, anemia is often underdiagnosed and undertreated. A recent study by Khan et al. on UC patients using a nationwide VA database in the USA showed that more than a third of anemic UC patients were not tested for IDA and among those tested and diagnosed with IDA, a quarter were not treated with iron replacement therapy [21]. Our aim of this paper was to discuss the various types of anemias in IBD patients, review the literature on this subject and provide a practical approach for the practicing physicians for early diagnosis of anemia as well as accurate and timely treatment of the same which will hopefully help reduce the prevalence and subsequent complications associated with the presence of anemia among IBD patients.

Definition of anemia

A patient's hemoglobin level is not a constant variable; it varies with age and gender. Other factors such as pregnancy, high altitudes, smoking and ethnicity

can also influence it [22, 23]. In view of this, we follow the WHO criteria used to define anemia (Table 1).

Different causes of anemia in IBD

Anemia in IBD is characterized by a multifactorial etiology (Table 2) [25]. These etiologies often overlap with each other and it is important to know the pathogenesis of each etiology for their optimum management.

Iron deficiency anemia (IDA)

IDA is the most common cause of anemia in IBD and reported in 36–90% of all anemic patients in IBD [15, 21, 25]. Iron deficiency anemia occurs when iron stores are exhausted and the supply of iron to the bone marrow is compromised. The various factors which causes IDA in IBD patients are (1) blood loss from the intestinal mucosal ulceration (common in UC), (2) decreased absorption of the iron secondary to surgical resection (common in CD), (3) reduced dietary intake and (4) inflammatory cytokines (IL-1, IL-6, TNF-A) mediated hepcidin overexpression which causes ferroportin degradation and consequential reduced iron release from the enterocytes to the blood stream [1, 14, 26].

Anemia of chronic disease (ACD)

The second major cause of anemia in IBD patients is ACD [27]. However, the exact prevalence of ACD in IBD is unknown, as it often correlates with IDA. Its pathophysiology remains complex and it is believed to be caused by the immune dysregulation secondary to pro-inflammatory cytokines (such as TNF, IL-1, IL-6, IFN-γ) seen in IBD. Five major mechanisms have been implicated in its etiology (i) decreased iron absorption from the gut and decrease release from the reticuloendothelial system due to cytokines induced hepcidin overexpression, (ii) reduced renal erythropoietin (EPO) release resulting in decreased erythropoiesis, (iii) interfering with EPO signaling process and downregulating EPO receptors, thus resulting in "EPO resistance," (iv) decreased proliferation and defective maturation of the erythrocyte precursor cells, and (v) a reduced erythrocyte lifespan by enhancing erythrophagocytosis [28, 29].

Table 1. WHO criteria for minimum hemoglobin levels used to define anemia in people living at sea level [24]

Age or sex group	Healthy individuals	Mild anemia	Moderate anemia	Severe anemia
	Hb level [g/dL]	Hb level [g/dL]	Hb level [g/dL]	Hb level [g/dL]
Non-pregnant women and girls (≥ 15 years)	≥ 12.0	11.0–11.9	8.0–10.9	< 8.0
Pregnant women (≥ 15 years)	≥ 11.0	10.0–10.9	7.0–9.9	< 7.0
Men (≥ 15 years)	≥ 13.0	11.0–12.9	8.0–10.9	< 8.0

Table 2. Causes of anemia in IBD [25]

Common	•Iron deficiency anemia •Anemia of chronic disease
Occasional	•Vitamin B_{12} deficiency •Folate deficiency •Drug-induced (sulfasalazine, thiopurines)
Rare	•Autoimmune hemolysis •Myelodysplastic syndrome •Aplasia (often drug-induced) •Innate hemoglobinopathies or disorders of erythropoiesis

Other types of anemia in IBD

Besides IDA and ACD, there can be various other causes of anemia in IBD patients.

Vitamin B12 deficiency anemia

Up to 22% patients with CD have vitamin B12 deficiency if diagnosis is based on serum levels; while the prevalence of B12 deficiency in UC is very low and has been comparable to the general population except those who underwent restorative proctocolectomy with ileo-anal pouch anastomosis [30•, 31]. The possible causes of vitamin B12 deficiency in IBD patients include (a) reduced absorptive capacity for B12 due to bowel resection, (b) bacterial overgrowth in the small bowel and proximal ileum, and (c) dietary intolerance [30•, 31].

Folic acid deficiency anemia

Folic acid deficiency is seen to be common in CD with a prevalence ranging from 16 to 28%, as compared to 1.4–12% in UC [32, 33]. The causes of folic acid deficiency in IBD patients include (a) side effect of sulfasalazine and methotrexate therapy, (b) inadequate dietary intake, (c) IBD disease activity and terminal ileum involvement, (d) consequence of vitamin B12 deficiency, since vitamin B12 plays a role in the conversion of inactive methyltetrahydrofolic acid to active tetrahydrofolic acid [34].

IBD therapy-related anemia

Drugs commonly used for IBD treatment such as sulfasalazine and thiopurines are often associated with anemia. Thiopurines, such as Azathioprine (AZA) and 6-Mercaptopurine (6-MP) may cause bone marrow suppression leading to pancytopenia, pure red cell aplasia and myelodysplastic syndrome (MDS), leading to macrocytic anemia [35–38]. Sulfasalazine has been associated with hemolytic anemia, medullary

aplasia and folate deficiency [39]. Methotrexate may also cause macrocytic anemia by folate deficiency or bone marrow suppression [40].

Autoimmune hemolytic anemia (AIHA)

Hemolytic anemia is more common in patients with UC than in patients with CD, with its prevalence range from 0.2 to 1.7% of UC patients [41]. AIHA can occur due to two main reasons (a) development of erythrocyte autoantibodies by crossed reactivity between surface colonocyte and RBC antigens and/or (b) sulfasalazine induced hemolysis in patients with Glucose-6-phosphate dehydrogenase deficiency [41, 42]. The course of hemolysis is unrelated to bowel involvement, and may develop before the occurrence of gastrointestinal symptoms [42].

Screening for anemia

Regular screening of IBD patients is essential due to factors like high prevalence, impact on quality of life and presence of comorbidities [43]. Based on ECCO (European Crohn's Colitis Organization) guidelines, complete blood count (CBC), serum ferritin, and C-reactive protein (CRP) should be assessed every 6–12 months in IBD patients with mild disease or in remission and every 3 months in patients with active disease [44••]. Serum levels of vitamin B12 and folic acid should be measured at least annually for patients at risk for vitamin B12 or folic acid deficiency (e.g. small bowel disease or resection), or if macrocytosis is present in the absence of thiopurine use [44••]. Patients with extensive small bowel resection, extensive ileal CD and patients who have undergone ileal-pouch and anastomosis surgeries are at an increased risk of vitamin B12 or folate deficiency and hence, these patients should be assessed more frequently than once a year [45].

Workup of anemia

Recently, the Crohn's and Colitis Foundation has developed an anemia care pathway for patients with IBD to help physicians manage anemia (Fig. 1). The workup for anemia in IBD patients should be performed if the hemoglobin is found to be below the normal range as defined by World Health Organization (WHO) on routine anemia screening ,Table 1 [44••, 47]. As per the ECCO recommendations, the initial standard workup consists of assessing the red blood cell indices such as mean corpuscular volume (MCV), reticulocyte count, differential blood count, red cell distribution width (RDW); serum ferritin; transferrin saturation (TSAT); and C-reactive protein (CRP) [44••]. MCV and reticulocytes helps to differentiate the different causes of anemia (Fig. 2). More extensive workup such as serum concentrations of vitamin B12, folic acid, haptoglobin, lactate dehydrogenase, soluble transferrin receptor (sTfR), percentage of hypochromic red cells (%HYPO), reticulocyte hemoglobin,

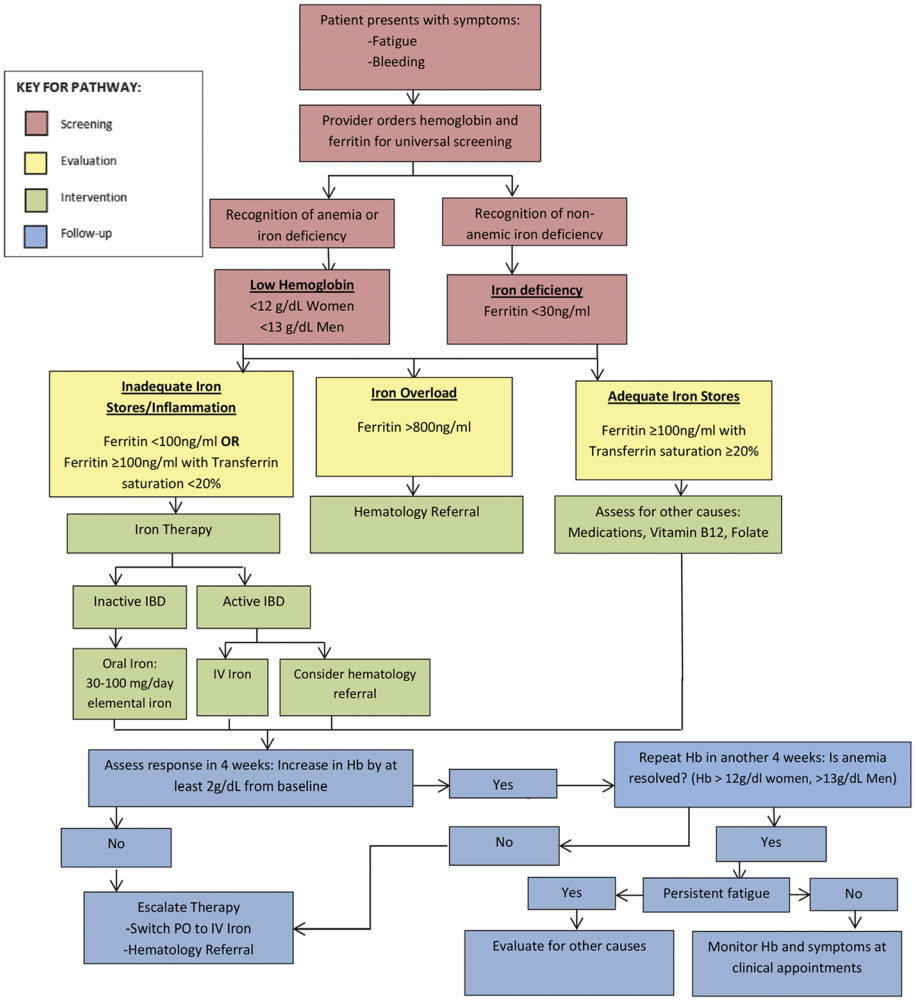

Fig. 1. Crohn's and Colitis Foundation of America (CCFA) anemia care pathway for patients with IBD [46].

bone marrow smear and creatinine is required if the above mentioned investigations fail to identify the cause of anemia, or if a therapeutic intervention is unsuccessful.

Diagnosis of anemia

IDA and ACD are the two most frequent types of anemia in IBD patients and as these conditions frequently co-exist and overlap with each other; their differentiation often poses a great challenge. The magnitude of this challenge is represented by the fact that the choice of the appropriate treatment for anemia in IBD is based on differentiating between IDA and ACD. IDA is characterized by low serum ferritin levels, while ACD is defined by elevated levels of ferritin in the setting of inflammation/infection and correlates with high inflammatory markers such as CRP and ESR.

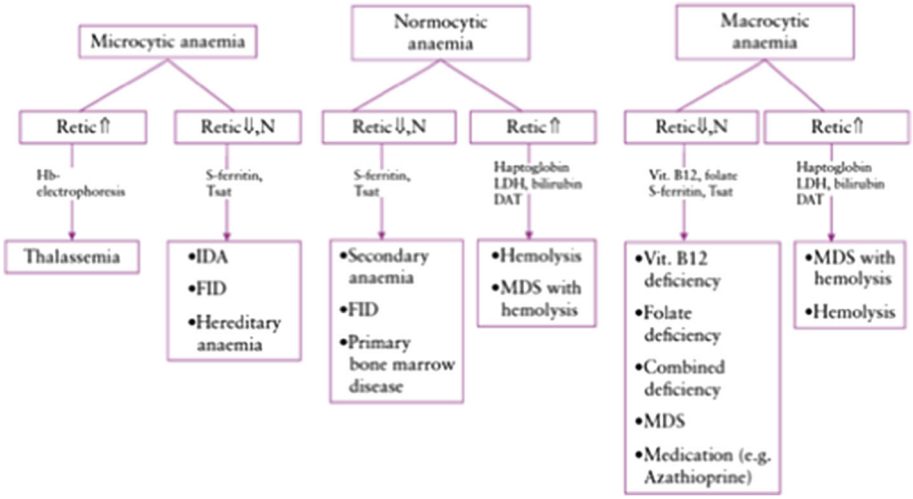

Fig. 2. Classification of anemia based on MCV and reticulocytes [44••]. Anemia can be effectively classified by using a combination of MCV and reticulocytes. Micro-, normo- and macrocytic anemias cover all forms of anemia, and the reticulocyte count tells whether the bone marrow can respond by increasing erythropoiesis, which gives early and important information on the direction of the investigation. All deficiency states are excluded by increased reticulocytes, Retic, reticulocyte count; N, normal; Tsat, transferrin saturation; LDH, lactate dehyrogenase; MCV, mean corpuscular volume; DAT, direct antibody test; Hb, hemoglobin; IDA, iron deficiency anemia; FID, functional iron deficiency; MDS, myelodysplatic syndrome; N, normal; S-ferritin, serum ferritin; Tsat, transferrin saturation; •anemia secondary to malignancy, infection, kidney disease etc.

IDA

Iron deficiency anemia is defined as anemia with biochemical evidence of iron deficiency. In the absence of inflammation, serum ferritin is the most accurate predictor of bodily iron stores [48]. However, existing literature states that ferritin being an acute-phase reactant can be falsely normal or elevated in inflammatory conditions [4]. The ECCO guidelines define IDA as serum ferritin < 30 μg/L in patients without clinical, endoscopic, or biochemical evidence of active disease. However, in the presence of inflammation, a serum ferritin up to 100 μg/L may still be consistent with iron deficiency [44••]. TSAT is an important marker of iron availability for hematopoiesis as it is less affected by inflammatory reactions [14, 49]. TSAT level 16–50% is considered as normal iron stores and TSAT level $< 16\%$ is considered as iron deficiency [25]. TSAT, although it is considered to be a reliable marker of iron status, is tested only in 25% of IBD patients with anemia [14].

In uncertain cases as to whether a patient has IDA or ACD sTfR, sTfR/ferritin ratio, percentage of hypochromic red cells and reticulocyte hemoglobin can also be used to determine the iron stores [50]. The sTfR measurement is advantageous because it inversely correlates with the amount of iron available for erythropoiesis and unlike ferritin; chronic inflammation has no effect on sTfR levels [51, 52]. Also, high sTfR level and sTfR/ferritin ratio > 1.4 favors true iron deficiency [53]. Recent studies including a meta-analysis showed that the sTfR and sTfR/log ferritin index are able to distinguish between IDA and ACD with a high diagnostic accuracy [53, 54].

ACD

ACD is characterized by mild to moderate anemia (Hb < 8 g/dL is rare), normal or reduced mean corpuscular volume (MCV), reduced serum iron and normal to elevated serum ferritin. In addition, it is also characterized by reticuloendothelial system (RES) stores that are elevated relative to total body iron, occurring in the setting of inflammatory disease [28]. In clinical setting, ACD may exist with or without functional iron deficiency (FID). A state of functional iron deficiency is produced when iron export from macrophages is reduced through reduction of ferroportin as a result of inflammatory cytokines induced hepcidin overexpression, which in turn reduces the transferrin saturation and iron transport to erythroblasts [44••]. The ECCO guideline states that in the presence of biochemical or clinical evidence of inflammation i.e. ACD with FID is likely if the serum ferritin is above 100 μg/L and the transferrin saturation is below 20%. In addition, serum ferritin between 30 and 100 μg/L represents a combination of true iron deficiency and ACD [44••].

The MCV may be low or normal in ACD. MCV level is usually normal irrespective of the presence or absence of FID. Low reticulocyte counts are seen in ACD with or without FID. The sTfR/log serum ferritin may be useful to exclude true iron deficiency if the ratio is less than 1 [28, 55].

Vitamin B12 and folate deficiency anemia

A patient with macrocytic anemia or anemia unresponsive to iron or erythropoietin is the prime suspect for vitamin B12 deficiency. Cobalamin and folate deficiency may occur in IBD, especially after ileal resection. ECCO suggests that cobalamin level and folate levels should be checked at least annually or when macrocytosis is present, in absence of thiopurine usage [44••]. Vitamin B12 deficiency is diagnosed when the serum level of vitamin B12 is below 200 pg/mL (140 pmol/L) along with clinical evidence of disease [56]. When the diagnosis is uncertain, homocysteine or methyl malonate levels can be measured. Increased homocysteine level indicates tissue deficiency of either B12 or folate with a greater sensitivity than serum B12 measurement. Methyl malonate is specific for B12 deficiency and likewise has a better sensitivity [57–59].

IBD therapy-related anemia

5-ASA derivatives, azathioprine and 6-mercaptopurine may affect the erythropoiesis as described in pathogenesis section. Drug induced anemia in IBD patients should be considered if any other satisfactory cause of anemia cannot be determined and if the patient is any one of these medications.

Treatment of anemia

Treatment of anemia in the IBD should be based on the underlying etiology of the anemia. Thus, it is important to identify the underlying etiology first.

Treatment of iron deficiency anemia

Correction of anemia improves the quality of life in patients with IBD, regardless of the disease activity [17, 19, 20]. As per recent ECCO guidelines, iron

supplementation is recommended for all IBD patients as soon as IDA is diagnosed by routine laboratory marker, such as Hb, CRP, and ferritin or transferrin saturation as described above [44••]. The benefit of treatment for iron deficiency (ID) without overt anemia has not been demonstrated in the IBD population; although in non-IBD patients, studies have shown improvement in fatigue, athletic performance in non-anemic female as well as in patients with CHF [60–63].

The major goal of IDA therapy is improvement in the quality of life by normalizing Hb and replenishing iron stores as well as relieving anemia-related symptoms [44••]. The criteria for 'a good response to treatment' is an increase in Hb levels > 2 g/dL within 4 weeks [64].

The treatment for IDA can be divided into 2 basic categories i.e. oral and intravenous (IV) iron formulations, both of which have their strengths and weaknesses. The presence of symptoms, the severity of anemia, the rate of Hb decline and the potential adverse effects of the therapy are the factors that determine the route of iron supplementation [25].

Oral iron supplements

The existing literature shows that oral and IV iron therapy are both equally effective in correcting mild anemia [65, 66]. Oral iron supplementation is generally considered standard first-line therapy for mild iron-deficiency anemia, defined as Hb levels of 11.0–11.9 g/dL in non-pregnant women and 11.0–12.9 g/L in men. This is due to the convenience and low cost of oral iron therapy [44••].

Oral iron supplements are available as either ferrous (Fe2+- such as ferrous fumarate, ferrous sulfate, and ferrous gluconate) or ferric (Fe3+- ferric iron polymaltose complex) salts. Several large clinical studies comparing ferrous sulfate preparations with ferric iron polymaltose complex preparations showed that ferrous sulfate remains the established and standard treatment of ID, irrespective of the indication, due to their good bioavailability, efficacy, and acceptable tolerability [67–69]. Recently, an oral iron compound called ferric maltol is believed to allow more efficient uptake of elemental iron into enterocytes. In addition, it also has a safer gastrointestinal profile compared to the ferrous formulations [70]. A significant improvement in Hb concentration by 2.25 g/dL was observed in a phase 3 clinical trial in which IBD patients intolerant or unresponsive to ferrous preparations were treated with ferric maltol for 12 weeks [70]. Schmidt C et al., in another study, evaluating the efficacy and safety of ferric maltol in IBD patients, showed that among the IBD patients unresponsive or partially responsive to oral iron therapies, 80% achieved normal Hb levels and increased iron stores after using ferric maltol with no issues related to tolerability [71]. This is considered a clinically significant change based on current guidelines for the management of IDA in IBD.

The recommended daily dose for adults with ID is 100 to 200 mg of elemental iron [60]. Absorption of oral iron therapy may be enhanced on addition of vitamin C. Stoffel et al. confirmed that that low-dose iron (60 mg) given on alternate days may reduce hepcidin level, maximize fractional iron absorption, increase dosage efficacy, reduce gastrointestinal exposure to unabsorbed iron, and ultimately improve tolerance of iron supplements in women with depleted iron stores [72].

The major factor compromising the efficacy and adherence of oral iron replacement, especially in the elderly IBD population, is the associated gastrointestinal side effects including nausea, flatulence, diarrhea and gastric erosion [73, 74]. It has been shown that within 2 months of therapy, the adherence lowers to 10–32% [73]. Also, polypharmacy such as antacids, H_2-blockers, proton pump inhibitors and diet such as quinolone, phytates from bran and tannates from tea may limit oral iron absorption [75–78]. Furthermore, hepcidin is increased in the setting of inflammation which prevents the transfer of intracellular oral iron. Moreover, studies have shown that non-absorbed iron can cause potentially harmful modification of the gut microbiota, increasing the concentration of intestinal pathogens in both children and adults and thereby enhancing intestinal inflammation [79].

The efficacy of administering oral iron therapy should be evaluated serially when given to patients. Okam et al. reported that a Hb increase of 1.0 g/dL or more at day 14 after starting oral supplementation may be the most accurate predictor of sustained treatment response [80]. IV iron therapy is the subsequent choice in patients with an inadequate response to oral iron.

IV iron therapy

The indications for IV iron therapy are patients with clinically active IBD, intolerance to oral iron, Hb level below 10 g/dL and/or in patients who need erythropoiesis stimulating agents (ESAs) [43].

The most important factor for consideration of IV iron preparations for IBD associated anemia is the fact that it bypasses the need for gastrointestinal absorption. It is safer, more effective, shows a faster response, and better tolerated than oral iron [20, 81–84]. However, the past experience of high molecular weight iron dextran (HMWID)-related anaphylactic reactions, in particular, has led to the general underutilization of intravenous iron preparations [85, 86]. Over the recent years, new, well-tolerated intravenous iron formulations have been developed with an increased safety profile [86]. However, except LMW iron dextran, these new preparations due to the reduced risk of releasing free iron to the blood and lack of acute toxicity do not require test dosing. US Food and Drug Administration (FDA) studying serious adverse reactions in new iv iron preparations showed a cumulative rate of only < 1:200,000 [87].

The six main formulations of IV iron, available and extensively studied in different IBD trials, i.e. low-molecular weight iron dextran, iron sucrose, ferric gluconate, ferric carboxymaltose, iron isomaltoside-1000 and ferumoxytol are equally efficacious in treating iron deficiency [20, 50, 88–92]. The major distinguishing factors among them include cost, formulary/purchasing agreements, and number of visits/time required to administer the full dose. They also differ by complex chemistry and can be grouped into labile, semi-labile and stable iron complexes [93]. A recent study evaluating the different iron formulations demonstrated that Ferric carboxymaltose was shown to be the most effective, followed by iron sucrose, iron isomaltose and oral iron on comparing the efficacy and tolerability of the various IV formulations [94]. The adverse event rates for ferric carboxymaltose, iron sucrose, iron dextran and iron isomaltose were 12.0%, 15.3%, 12.0% and 17.0% respectively [94]. Evstatiev et al., in a multinational randomized study, found that Ferric carboxymaltose

was superior to iron sucrose in terms of efficacy [20]. Ferric carboxymaltose and iron isomaltoside are the formulations of choice if high iron doses and speedy iron replenishment are desired [95, 96].

The Ganzoni formula (iron deficit [mg] = body weight [kg] × (target Hb – actual Hb [g/dL]) × 2.4 + 500 mg) is used for calculating the dosages of parenteral iron [97]. However, the drawbacks of this formula are that it is inconvenient, inconsistently used in everyday clinical practice, and it underestimates the true iron requirements. A simpler fixed-dose regimen (of ferric carboxymaltose) based on Hb and body weight was tested in IBD patients and found superior to the Ganzoni-calculated dosing (of iron sucrose) in terms of efficacy and compliance [20].

In spite of the excellent safety profile of new IV iron formulations, they are associated with non-allergic infusion reactions including self-limiting urticaria, palpitations, dizziness, and neck and back spasm in < 1% of individuals and do not progress to more serious reactions [98]. A transferrin saturation above 50% and serum ferritin above 800 μg/L should be used as upper limits for guiding therapy, to alleviate the risk of iron overload [14]. Intramuscular iron is obsolete as injections are painful, damaging to tissues and are associated with unacceptable side effects [99].

Treatment and prevention of recurrent IDA

Despite effective intravenous iron supplementation, IDA recurs in more than 50% of patients within 10–12 months [92]. The post treatment iron stores as reflected by serum ferritin is the factor determining the time to recurrence of IDA [51]. Post-treatment serum ferritin levels of > 400 μg/L prevented recurrence of iron deficiency within the following 1–5 years better than any levels below this value. Hence, the aim for intravenous IV replacement was suggested to be ferritin levels up to 400 μg/L [51].

The recommendation for monitoring Hb indices and iron status is every 3 months for at least 1 year after anemia correction, and every 6–12 months once Hb normalizes and iron stores are replenished. Hb, ferritin, TSAT and CRP can be utilized for this [44••]. In contrast to the traditional "watch and wait" strategy, the FERGImain and the PROCEEDextend trial both impressively demonstrated that the recurrence of IDA in IBD patients can be prevented by re-treatment with intravenous iron (500 mg of ferric carboxymaltose) as soon as serum ferritin drops below 100 μg/L or hemoglobin below 12 or 13 g/dL (according to gender) [81, 100]. The cost analysis also favors such a proactive approach of anemia prevention [101].

Rapid recurrence of IDA should also raise suspicion of underlying subclinical inflammatory activity and the long-term effect to alleviate anemia depends on the ability to adequately control bowel inflammation [102]. Endoscopy should be done to evaluate disease activity in patients with a low CRP as disease activity is not always associated with increase in acute phase proteins and clinical symptoms [15, 25, 103].

ACD treatment

Persistent inflammation plays an important role in the pathophysiology of ACD by altering iron metabolism, erythropoiesis, and erythrocyte survival, and

the most important step is to induce complete remission [28, 103]. It was shown that the anti-TNF-therapy improves hematologic markers in treated patients [13, 104]. Pro-inflammatory cytokines (such as TNF) decrease erythropoiesis and thus, it makes sense in concluding that anti-TNF therapy may improve anemia by inducing erythropoiesis [13, 104]. However, healing of the ulcerated mucosa and reducing blood loss has also been hypothesized for improvement of anemia [103].

IV preparations are superior to oral iron in conditions requiring rapid Hb increase or ACD with FID. ESAs are the reserved choice for patients who do not respond satisfactorily to IV iron and in whom disease activity is adequately controlled [25, 44••]. ESAs should always be combined with intravenous iron supplementation because functional iron deficiency is likely to develop [3]. Several studies have shown that a majority of patients with IBD respond to ESA treatment with an increase in hemoglobin and improvement of quality of life [105–108]. To minimize adverse outcomes (venous thrombosis and/or cardiovascular events), treatment is limited to maximal hemoglobin of 12 g/dL in cancer or renal insufficiency.

Vitamin B12 deficiency and folate deficiency treatment

In patients with vitamin B12 deficiency, adequate supplementation of vitamin B12 is important. The endpoints should be resolution of megaloblastic anemia, improvement in myelopathy, and normalization of serum B12 level or MMA (methyl malonic acid) [109]. The recommendations regarding dosage and timing of vitamin B12 supplementation are largely inconsistent in patients with IBD. However, parenteral (intramuscular or subcutaneous) administration remains the preferred route in the case of existing vitamin B12 deficiency. Patients with severe vitamin B12 deficiency with/without clinical symptoms should receive 1000 mcg of parental B12 every other day for 1 week and then weekly until clinically improved, followed by monthly injections for life [109]. Correction of megaloblastic anemia may take up to 8 weeks. Those with ileal resections greater than 20 cm must receive lifelong replacement [109]. Oral therapy may be as effective, but is underexplored in CD [109]. Adverse reactions include nausea, flushing, pruritus, fever, dizziness, exanthema and (rarely) anaphylaxis [109]. A reticulocyte response should be evident after 7–10 days and if a hematological response is not achieved, the initial diagnosis should be reviewed [109]. Suboptimal response may indicate previously masked iron and/or folic acid deficiency or the presence of another co-existing cause of anemia [34].

In patients with megaloblastic anemia secondary to folic acid deficiency, the first step is to exclude underlying vitamin B12 deficiency [34]. After excluding vitamin B12 deficiency, folic acid supplementation should be initiated with 5 mg folic acid daily for 4 months. A total of up to 15 mg folic acid daily for 4 months is suggested in malabsorptive states [34].

Future direction in management of anemia in IBD

Hepcidin plays a major role in the pathophysiology of ACD in IBD. In iron deficiency anemia, the transcription of hepcidin is suppressed to

facilitate the absorption of iron and the release of iron from body stores. While in ACD, the level of hepcidin is elevated since it is an acute phase reactant [110]. Hence, hepcidin could potentially be used to distinguish IDA and ACD. Further studies are warranted on detecting hepcidin level in the body and finding its cut-off value to differentiate ACD and IDA. Drugs targeting hepcidin are in the development and could change the treatment algorithm in ACD. Currently, those drugs could be split into 3 groups: hepcidin production suppressors, hepcidin neutralizing agents, and hepcidin-ferroportin interfering agents. IL-6 is one of the factor that upregulates hepcidin level. Tocilizumab, the anti-IL-6 receptor antibody, has been studied in monkeys to reduce hepcidin expression and therefore, improvement in arthritis-related anemia [111]. Recently, LY2787106, hepcidin neutralizing monoclonal antibody, has shown dose-dependent improvement in serum iron and transferrin saturation in patients with cancer-related anemia [112]. Another monoclonal antibody (LY2928057) targeting ferroportin, prevents hepcidin from binding to the transporter without affecting the iron efflux, exhibited promising results on cynomolgus monkeys, and phase I trials are on their way for this drug [113].

Conclusion

Anemia is the most common systemic complication and extra-intestinal manifestation of inflammatory bowel disease. Anemia impairs patient's QOL and increases health-care burden by its association with frequent hospitalization. Although there are several causes of anemia in IBD, the two most frequent causes are iron deficiency anemia (IDA), and anemia of chronic disease (ACD). Regular screening of anemia is important in patients with IBD. Once anemia is diagnosed, detailed evaluation of anemia using adequate laboratory indices is essential to differentiate between the different types of anemia. The cornerstone of anemia management depends on underlying etiology along with normalization of IBD activity. Iron supplementation is recommended in all IBD patients when IDA is present and IV route is recommended in patients with clinically active IBD, with previous intolerance to oral iron, with hemoglobin below 10 g/dL, and in patients who need erythropoiesis-stimulating agents. After proper treatment of anemia, the monitoring for recurrent anemia is equally essential in the course of therapy.

Compliance with Ethical Standards

Conflict of Interest

Dhruvan Patel declares that he has no conflict of interest. Chinmay Trivedi declares that he has no conflict of interest. Nabeel Khan declares that he has no conflict of interest.

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

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