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ECCO Guideline/Consensus Paper

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European Consensus on the Diagnosis and Management of Iron Deficiency and Anaemia in Inflammatory Bowel Diseases

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1. Introduction

Anaemia is the most common systemic complication and extraintestinal manifestation of inflammatory bowel disease [IBD].[1–3] In the majority of cases, IBD-associated anaemia is a unique example of the combination of chronic iron deficiency and anaemia of chronic disease [ACD].[4,5] Other more rare causes of anaemia in IBD include vitamin B_{12} and folate deficiency, toxic effects of medications, and others. The impact of anaemia on the quality of life of IBD patients is substantial. It affects various aspects of quality of life such as physical, emotional, and cognitive functions, the ability to work, hospitalization, and healthcare costs.[6] Anaemia in IBD is not just a laboratory marker; it is a complication of IBD that needs appropriate diagnostic and therapeutic approaches.[3]

Despite the broad use of anti-inflammatory therapy, anaemia may recur fast after successful therapy. As anaemia is a serious medical condition that may become life threatening [if blood transfusions are not available or compatible], preventive measures should be considered. Prevention of anaemia and maintenance of iron and vitamin stores are therefore warranted.

The goal of this consensus initiated by the European Crohn's and Colitis Organisation [ECCO] was to establish European consensus guidelines for the diagnosis, treatment and prevention of iron deficiency and iron deficiency anaemia [IDA], but also for non-iron deficiency anaemia and associated conditions.

The consensus is based in parts on a previous evidence-based consensus publication on the diagnosis and management of iron deficiency and anaemia in inflammatory bowel diseases.[7] The strategy to reach the consensus involved several steps and follows the standard operating procedures for consensus guidelines of ECCO. An open call for chairs and participants for this consensus was made [see acknowledgements and www.ecco-ibd]. Participants

were selected by the Guidelines Committee of ECCO [GuiCom] on the basis of their publication record and a personal statement. Four working groups [WGs] were formed: WG 1 on Diagnosis of anaemia, WG 2 on Treatment of iron deficiency anaemia, WG 3 on Prevention of iron deficiency anaemia, and WG 4 on Management of non-iron deficiency anaemia. Participants were asked to answer relevant questions on current practise and areas of controversy related to the diagnosis and management of anaemia in IBD based on their experience as well as evidence from the literature [Delphi procedure].[8] In parallel, the WG members performed a systematic literature search of their topic with the appropriate key words using Medline/PubMed/ISI/Scopus and the Cochrane database, as well as their own files. The evidence level [EL] was graded according to the Oxford Centre for Evidence-Based Medicine.[9] Provisional guideline statements [with supporting text] were then written by the WG chairs, based upon answers to the questionnaire, and were circulated among the WG members, prompting discussions and exchange of literature evidence. The proposed statements and the supporting text were submitted to an online platform for online discussion and two online voting procedures, among all consensus participants for the first voting procedure and also for all national representatives of ECCO for the second voting procedure. The WGs finally met in Frankfurt on June 28, 2013 for a face-to-face discussion and to vote and consent on the statements. Technically this was done by projecting the statements and revising them on screen until a consensus was reached. Consensus was defined as agreement by more than 80% of participants, termed a Consensus Statement and numbered for convenience in the document. The final manuscript was written by the WG chairs in conjunction with the WG members and was revised for consistency by CG and AD. An update of this current consensus guideline is planned in about 4 years.

2. Diagnosis of Anaemia

2.1. Definition of anaemia

2.1.1. ECCO Anaemia Statement 1A

The currently used WHO definition of anaemia [Table 1] applies also to patients with IBD. All patients with IBD should be assessed for the presence of anaemia. The major forms of anaemia in IBD are iron deficiency anaemia, anaemia of chronic disease and anaemia of mixed origin [EL 5]

Table 1. Minimum hemoglobin and hematocrit levels used to define anaemia in people living at sea level.[10]

Age or sex group	Hemoglobin		Hematocrit
	[g/dL]	[mmol/dL]	[%]
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
Nonpregnant women	12.0	7.45	36
Pregnant women	11.0	6.83	33
Men	13.0	8.07	39

Normal hemoglobin varies with age and gender. Also other factors influence hemoglobin levels such as pregnancy, high altitudes, smoking, and ethnicity.[11,12] The lower limits of normal hemoglobin concentration are even lower in African Americans [11.5 g/dL for women, 12.9 g/dL for men] and in the elderly. Interpretation of hemoglobin and hematocrit levels needs to consider such modulating factors. The definitions of anaemia in IBD is indifferent to other conditions and it is reasonable that WHO cut-offs apply.[10] IBD patients should be regularly assessed for the presence of anaemia because of its high prevalence, its impact on quality of life, and comorbidity.[13] About two-thirds of such patients have anaemia at diagnosis. During follow-up the prevalence and causes of anaemia may change.[14] In children anaemia is even more common [about 70%] than in adults [about 30–40%].[15]

2.2. Screening parameters

2.2.1. ECCO Anaemia Statement 1B

For laboratory screening, complete blood count, serum ferritin, and C-reactive protein [CRP] should be used. For patients in remission or mild disease, measurements should be performed every 6 to 12 months. In outpatients with active disease such measurements should be performed at least every 3 months [EL 5]. Patients at risk for vitamin B_{12} or folic acid deficiency [eg small bowel disease or resection] need proper surveillance. Serum levels of vitamin B_{12} and folic acid should be measured at least annually, or if macrocytosis is present in the absence of thiopurine use [EL 4]

The risk of developing anaemia relates to disease activity, because both blood loss and ACD are triggered by intestinal inflammation. Complete [or full] blood count, CRP, and serum ferritin are minimum requirements to detect anaemia, an inflammatory flare, or iron deficiency at an early stage. Diagnostic measurement of complete blood counts and CRP has been part of previous recommendations in IBD.[7,16] The recommended timelines are based on expert opinion and reflect common clinical practice, but do not apply to hospitalized patients. In patients with extensive small bowel resection, extensive ileal Crohn's disease, ileal-anal pouch, evidence of vitamin B_{12} or folic acid deficiency should be assessed more frequently than once a year.[17]

2.3 Anaemia workup

The purpose of these recommendations is to set an appropriate threshold to trigger action, and to advise on necessary tests. The initial workup of anaemia should follow a simple algorithm widely used in hematology [Figure 1]. Starting from the evaluation of MCV, the most common causes of anaemia in IBD may be recognized: microcytosis

2.3.1 ECCO Anaemia Statement 1C

Anaemia workup should be initiated if the hemoglobin is below normal. The minimum workup includes red blood cell indices such as red cell distribution width [RDW] and mean corpuscular volume [MCV], reticulocyte count, differential blood cell count, serum ferritin, transferrin saturation [TfS], and CRP concentration. More extensive workup includes serum concentrations of vitamin B_{12}, folic acid, haptoglobin, the percentage of hypochromic red cells, reticulocyte hemoglobin, lactate dehydrogenase, soluble transferrin receptor, creatinine, and urea [EL 4]. Advice from a hematologist is appropriate if the cause of anaemia remains unclear after more extensive workup [EL 5]

indicates iron-restricted anaemia [true or functional iron deficiency], macrocytosis may indicate B_{12} or folate deficiency, and normocytosis anaemia of chronic disease [ACD]. Thus, the MCV and mean corpuscular hemoglobin [MCH] are useful variables and available within the complete blood count. In ACD, they may be normal or low.[18] Macrocytosis is indicative of vitamin deficiency, but also arises from thiopurine treatment [azathioprine or 6-mercaptopurine], other medications, alcohol abuse, hypothyroidism, or reticulocytosis.

In the next step, reticulocyte count is considered. Low or 'normal' reticulocytes indicate inability to respond properly to anaemia, either because of deficiencies that result in inappropriate erythropoiesis or primary bone marrow disease. Increased reticulocytes indicate increased red cell formation and therefore exclude deficiencies. Instead, hemolysis should be sought after by estimation of serum concentrations of haptoglobin, lactate dehydrogenase, and bilirubin. The minimum workup should include complete blood count with MCV, reticulocytes, serum ferritin, transferrin saturation, and CRP. In accordance with the algorithm in Figure 1, more extensive workup may include vitamin B_{12}, folic acid, haptoglobin, a differential white blood cell count, and bone marrow smear.[19] A comprehensive list of anaemias classified with MCV and reticulocytes is given in Table 2. In some situations microcytosis and macrocytosis co-exist, so that the two abnormalities may neutralize each other and result in a normal MCV. A wide size range of the red cells [high RDW] can help in this situation, as RDW is an indicator of iron deficiency.[19,20]

Platelet and white blood cell counts are also available within the complete blood count and help to distinguish isolated anaemia from pancytopenia. A truncated, soluble form of the transferrin receptor circulates in the plasma and its concentration is directly proportional to the total body mass of cellular transferrin receptor.[22] It is elevated in plasma in situations where the bone marrow needs more iron, both in elevated erythropoietic activity and in iron deficiency [true or functional]. An elevated soluble transferrin receptor [sTfR] is a good indicator of iron-deficient erythropoiesis, particularly helpful in the detection of iron deficiency in the presence of inflammation [with normal or even elevated serum ferritin].[18] The percentage of hypochromic red cells, the hemoglobin concentration of reticulocytes, and the red blood cell size factor are also useful markers for the diagnosis of iron-restricted erythropoiesis.[4,20] Red blood cell size factor is a new parameter which combines the volume of erythrocytes and the volume of reticulocytes. Since disease activity is not always associated with an increase in acute phase proteins [particularly in ulcerative colitis] and may not be accompanied by clinical symptoms, endoscopy may be needed to evaluate disease activity in patients with a low or negative CRP.

2.4. Iron deficiency

2.4.1. ECCO Anaemia Statement 1D

Diagnostic criteria for iron deficiency depend on the level of inflammation. In patients without clinical, endoscopic, or biochemical evidence of active disease, serum ferritin <30 µg/lL is an appropriate criterion [EL 2]. In the presence of inflammation, a serum ferritin up to 100 µg/L may still be consistent with iron deficiency [EL 4]

In IBD, the distinction between iron deficiency anaemia and ACD is important, since both conditions typically overlap. In the management of IBD patients with anaemia, the choice of the appropriate treatment is based on this distinction. Iron deficiency may be caused by continuous blood loss from the ulcerated surface of the bowel, malnutrition with reduced iron intake, or impaired iron uptake through the duodeno-jejunal mucosa. In the absence of biochemical [CRP, ESR, leukocyte count] or clinical evidence [diarrhoea, hematochezia, endoscopic findings] of inflammation, iron deficiency is likely if the serum ferritin is <30 µg/L. In the presence of inflammation, serum ferritin levels can be

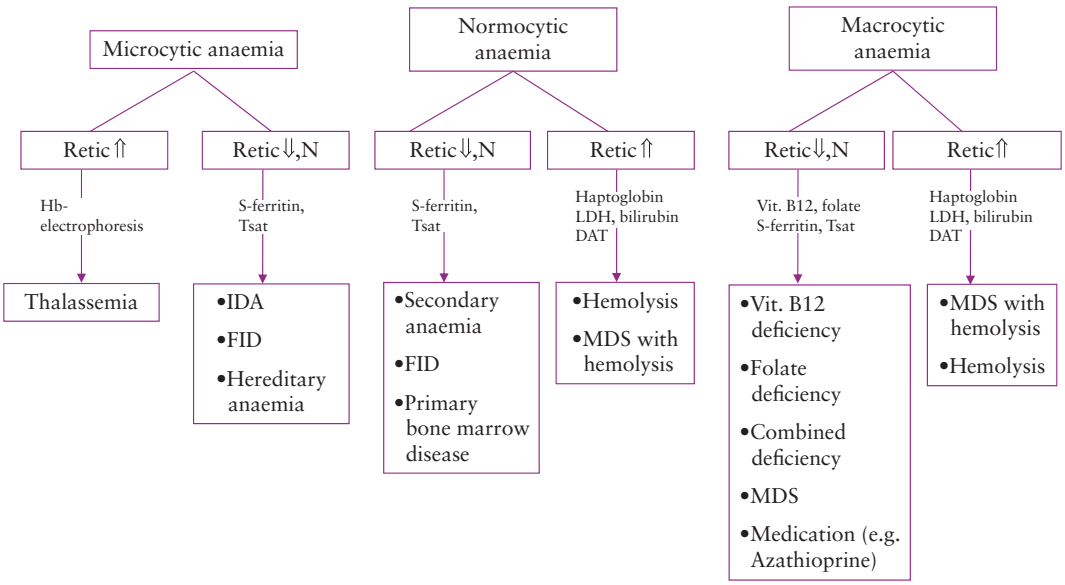

Figure 1. Anaemia classification based on MCV and reticulocytes. Anaemia can be effectively classified by using a combination of MCV and reticulocytes. Micro-, normo- and macrocytic anaemias cover all forms of anaemia, and the reticulocyte count tells whether the bone marrow can respond by increasing 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 dehydrogenase; MCV, mean corpuscular volume; DAT, direct antibody test; Hb, hemoglobin; IDA, iron deficiency anaemia; FID, functional iron deficiency; MDS, myelodysplastic syndrome; N, normal; S-ferritin, serum ferritin; Tsat, transferrin saturation; *anaemia secondary to malignancy, infection, kidney disease etc.

Table 2. Classification of anaemia by MCV and reticulocytes [adapted from reference[21]].

Microcytic anaemia with normal or low reticulocytes
Iron deficiency
Anaemia of chronic disease [cancer, infection,...]
Lead poisoning [very rare]
Hereditary microcytic anaemia [rare]
Microcytic anaemia with elevated reticulocytes
Hemoglobinopathies [thalassaemia...]
Normocytic anaemia with normal or low reticulocytes
Acute hemorrhage [may initially have elevated reticulocytes]
Renal anaemia [endogenous erythropoietin levels = inappropriately low]
Anaemia of chronic disease [cancer, infection…]
Severe aplastic anaemia [SAA], pure red cell aplasia [PRCA]
Primary bone marrow diseases [leukaemias, MDS diseases]
Bone marrow infiltration by cancer [prostate, breast...]
Combination of iron deficiency and B_{12}/folate deficiency [very rare, usually in malabsorption]
Normocytic anaemia with elevated reticulocytes
Hemolytic anaemia
Macrocytic anaemia with normal or low reticulocytes
Myelodysplastic syndrome [MDS]
Vitamin B_{12} deficiency [pernicious anaemia, *H. pylori* gastritis, antacids, vegans]
Folate deficiency [increased requirement in pregnancy, hemolysis, chronic myeloid leukaemia]
Long-term cytostatic medication [hydroxy-urea, methotrexate, azathioprine…]
Hypothyroidism
Alcoholism [isolated macrocytosis without anaemia]
Thiamine-responsive megaloblastic anaemia syndrome [very rare]
Macrocytic anaemia with elevated reticulocytes
Hemolytic anaemia [false macrocytosis]
Myelodysplastic syndrome with hemolysis

high despite empty iron stores.[23,24] In such cases, 100 µg/L is considered an appropriate cut-off level.[18,25] Up to 8 weeks after intravenous iron therapy, serum ferritin levels correlate less well with body iron stores; iron therapy induces ferritin synthesis and makes levels inappropriately high.[26] Iron deficiency without anaemia may cause an array of clinical, symptoms including fatigue, sleeping disorders, restless legs syndrome, attention deficit, discontentment, agitation, or female infertility.[27–29] The concentration of sTfR in the serum is an indicator of the iron supply available for erythropoiesis and, unlike ferritin, chronic inflammation has no effect on sTfR levels.[22] Recent studies including a meta-analysis showed that the sTfR and sTfR/log ferritin index are able to distinguish between iron deficiency anaemia and ACD with a rather high diagnostic accuracy.[30–32] The measurement of sTfR, percentage of hypochromic red cells and reticulocyte hemoglobin [the two latter measurements useful in the diagnosis of functional iron deficiency, see below] can be considered in uncertain cases.

2.5. Anaemia of chronic disease

2.5.1. ECCO Anaemia Statement 1E

In the presence of biochemical or clinical evidence of inflammation, the diagnostic criteria for ACD are a serum ferritin >100 µg/L and TfS <20%. If the serum ferritin level is between 30 and 100 µg/L, a combination of true iron deficiency and ACD is likely [EL 2]

The traditional term ACD includes all anaemia associated with and caused by chronic disease. Previous knowledge acknowledged the inhibitory effect of inflammation on erythropoietin response to anaemia as well as the direct inhibition of erythropoietic activity in the bone marrow. More recent research has also shown that inflammation has a profound effect on iron metabolism. In patients with active inflammation, various cytokines upregulate the production of hepcidin in the liver, which reduces iron export from macrophages into the reticuloendothelial system through reduction of ferroportin, thereby reducing transferrin saturation and iron transport to the erythroblasts, creating a situation of functional iron deficiency for erythropoiesis and reducing erythropoiesis. Inflammatory cytokines also reduce erythropoietin production and inhibit erythropoiesis.[18] The increase in hepcidin also reduces iron absorption from the duodenum.[33,34] The combined mechanisms may lead to ACD with functional iron deficiency [FID] and are common for many diseases with inflammation like cancer, IBD, rheumathoid diseases, and others. Functional iron deficiency is defined as a situation with normal or elevated iron stores, a reduced transport of iron from the macrophages, a low transferrin saturation in plasma and restricted iron availability in the bone marrow, which reduces erythropoiesis. ACD with FID is likely if the serum ferritin is above 100 µg/L and the TfS is below 20%. An increase in hypochromic red cells and/or a lowering of reticulocyte hemoglobin indicate FID, but as these measurements are not available in many centres, the diagnosis of FID usually is made from the combination of low Tsat and normal or elevated S-ferritin. In addition, the sTfR/log serum ferritin may be useful to exclude true iron deficiency [if the ratio <1].[18,30] MCV may be low or normal in ACD. If FID is not present, MCV is usually normal, but this may also be the case with FID. ACD ± FID always gives low reticulocyte counts.

However, not all IBD patients with anaemia show signs of FID. In an individual patient there may be all the above mechanisms involved in producing anaemia, but sometimes one aspect is less prominent or not detectable. Therefore, anaemia of chronic disease may exist with or without FID.

The following definitions are useful in this context:

1. Anaemia of chronic disease [ACD]: anaemia accompanying chronic disease and caused mainly by inflammatory mechanisms.
2. ACD with functional iron deficiency: ACD where FID can be diagnosed by low Tsat and normal or elevated S-ferritin [or increased levels of hypochromic red cells in blood].
3. ACD without FID: anaemia of chronic inflammatory disease without signs of FID.
4. Iron-restricted anaemia [IRA]: this definition is now widely used for any anaemia where the erythropoietic activity is reduced due to a restricted availability of iron in the bone marrow, either by true iron deficiency or FID.

3. Treatment of Iron Deficiency Anaemia

3.1. Initiation of iron supplementation

3.1.1. ECCO Anaemia Statement 2A

Iron supplementation is recommended in all IBD patients when iron deficiency anaemia [IDA] is present [EL 1]

Quality of life improves with correction of anaemia, and this improvement is independent of clinical activity.[35,36] The decision to supplement iron in patients without anaemia is more controversial and will depend on the patients' history, symptoms and individual preferences. Although there is evidence of benefit in treating iron deficiency without anaemia in other conditions such as chronic fatigue and heart failure, such evidence is not yet available in the context of IBD.[29,37,38]

3.1.2. ECCO Anaemia Statement 2B

The goal of iron supplementation is to normalize hemoglobin levels and iron stores [EL 1]

The lower the baseline hemoglobin, the longer is the time to normalization of hemoglobin. An increase in hemoglobin of at least 2g/dL within 4 weeks of treatment is an acceptable speed of response.[39]

3.2. Method of iron supplementation

3.2.1. ECCO Anaemia Statement 2C

Intravenous iron should be considered as first line treatment 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 [ESAs] [EL 1]

The usual treatment of iron deficiency anaemia [IDA] with oral iron has relevant limitations in IBD patients. Intravenous iron is more effective, shows a faster response, and is better tolerated than oral iron. Thus, intravenous iron preparations are preferred in the correction of IBD-associated anaemia and were recommended also in previous international guidelines.[7] Intravenous iron is safe, effective, and well tolerated both in the correction of IDA and maintenance of iron stores in patients with IBD.[36,40–43] Several intravenous iron preparations are currently available for treatment of IDA. Such formulations differ by complex chemistry and can be grouped into labile, semi-labile, and stable iron complexes.[44] Large published trials in IBD patients are available from iron sucrose,[36,39,45–51] ferric carboxymaltose[36,40–42,52] and iron isomaltoside 1000.[59] Single doses of up to 7 mg/kg iron sucrose have been tested;[48] repeated dosing is limited to 200–300 mg per treatment episode. For iron carboxymaltose, single doses are 500–1000 mg (up to 20 mg/kg body weight [BW]). The drug can be delivered within 15 min. Small data series are also available for ferumoxytol[53,54] which is licensed for use in chronic kidney disease and is currently undergoing Phase III trials in a number of other conditions associated with iron deficiency, including IBD [ClinicalTrials.gov identifier: NCT01114139, NCT01114217, and NCT01114204]. The currently available IV iron formulations are not created equal and there has been no direct comparison between different formulations.[35,38–41,44–54] Thus, a formal direct comparison of the currently available IV formulations with respect to efficacy, side effects, and other parameters seems not appropriate, as dose effects, patient selection, and other parameters in various trials are not comparable.

A test dose is required for iron dextran preparations as they carry a risk for serious anaphylactic reactions.[55,56] The risk of iron overload in patients who are chronically bleeding [such as in IBD] is intrinsically low, although a transferrin saturation above 50% and serum ferritin above 800 µg/L should be used as upper limits for guiding therapy.[4] Intramuscular iron is obsolete as injections are painful, damaging to tissues and are associated with unacceptable side effects.[57]

3.2.2. ECCO Anaemia Statement 2D

The estimation of iron need is usually based on baseline hemoglobin and body weight, and this is more effective for the treatment of IDA in IBD patients than individualized dosing based on the traditional Ganzoni's formula [EL 2]

Ganzoni's formula captures the total body iron deficit in milligrams (body weight in kg x [target hemoglobin-actual hemoglobin in g/dL] x 0.24 + 500).[58] However, the formula is inconvenient, prone to error, inconsistently used in clinical practice, and underestimates iron requirements.[41,59] The FERGIcor trial compared a novel and simple scheme [Table 3] with the Ganzoni-calculated dosing in anemic patients with IBD.[36] The simple ferric carboxymaltose dosing regimen showed better efficacy and compliance, as well as a good safety profile, compared with the Ganzoni-calculated iron sucrose dose regimen. In this clinical trial setting, the simple scheme has only been used for dosing of ferric carboxymaltose. In clinical practice, however, it is also used for dosing of other intravenous iron compounds. Limitations of this scheme include patients with hemoglobin below 7.0 g/dL, who likely need an additional 500 mg. Also, the estimation of iron needs in iron deficiency without anaemia is not covered. A minimum of 500–1000 mg should be considered.[38,40]

Table 3. Simple scheme for estimation of total iron need.[36]

Hemoglobin g/dL	Body weight <70 kg	Body weight ≥70 kg
10–12 [women] 10–13 [men]	1000 mg	1500 mg
7–10	1500 mg	2000 mg

3.2.3. ECCO Anaemia Statement 2E

Oral iron is effective in patients with IBD and may be used in patients with mild anaemia, whose disease is clinically inactive, and who have not been previously intolerant to oral iron [EL1]

Mild anaemia has been defined by the WHO as hemoglobin 11.0-11.9 g/dL in non-pregnant women and 11.0–12.9 g/L in men.[60] Some comparative studies indicate that oral iron may be as effective as intravenous iron in correcting hemoglobin.[41,47] However, a recent meta-analysis has reported a significant difference in ferritin and hemoglobin increment in favour of the intravenous route.[61]

Side effects from oral iron are dose dependent. Absorption of iron from the gastrointestinal tract is limited, and unabsorbed iron is exposed to the ulcerated intestinal surface.[2] Mucosal harm has been described in IBD.[62] Studies in animal models of IBD indicate that luminal iron may exacerbate disease activity,[63–65] induce carcinogenesis,[66] and alter intestinal microbiota.[67] In a recent study in African children, dietary iron supplementation affected microbiota and increased fecal calprotectin.[68] Most studies on oral iron were done with ferrous sulphate. Preliminary data on novel ferric formulations [such as ferric maltol] indicate effectiveness with a preferred adverse event profile, even in IBD patients with a history of intolerance to ferrous sulphate.[69]

3.2.4. ECCO Anaemia Statement 2F

No more than 100 mg elemental iron per day is recommended in patients with IBD [EL 2]

The daily absorption of iron from meals is 0.52 mg in adults. This can rise to 20 mg when iron stores are depleted and iron is supplemented.[70,71] In elderly and pregnant women, low-dose [20–100 mg] oral iron treatment is effective in correcting anaemia.[72,73] Low-dose ferric maltol in IBD is effective as well.[69] Higher doses are associated with more side effects and lower compliance.

4. Prevention of Iron Deficiency Anaemia

4.1. Monitoring for recurrent iron deficiency

4.1.1. ECCO Anaemia Statement 3A

Patients with IBD should be monitored for recurrent iron deficiency every 3 months for at least a year after correction, and between 6 and 12 months thereafter [EL 4]

After effective iron replenishment, anaemia recurs rapidly, ie by 50% within 10 months.[40,74] Therefore, patients with IBD should be monitored for iron deficiency every 3 months using a combination of hemoglobin, ferritin, transferrin saturation, and CRP.

4.1.2. ECCO Anaemia Statement 3B

Recurrent anaemia may be indicative of persistent intestinal disease activity even if there is clinical remission and inflammatory parameters [CRP etc] are normal [EL 5]

A good correlation exists between intestinal disease extent and activity on one side and the amount of blood loss and severity of anaemia on the other side.[75] Therefore, one important measure for prevention of anaemia recurrence is the treatment of the underlying disease.[2,76] Although apparently obvious, this step is sometimes difficult in clinical practice.[3] Moreover, the long-term effect to alleviate anaemia depends on the ability to adequately control bowel inflammation.[77,78] A rapid recurrence of iron deficiency in asymptomatic patients should spur the suspicion of a physician on subclinical inflammatory activity.

4.2. Preventive treatment for iron deficiency anaemia

4.2.1. ECCO Anaemia Statement 3C

The goal of preventive treatment is to maintain hemoglobin and serum ferritin levels within the normal range [EL 3]

Iron deficiency can cause symptoms and impair quality of life even when fully developed anaemia is not yet present.[36,38,75] In fact, it is rather common in everyday clinical practice to find iron deficiency as the only sign of disease activity in IBD patients. The decision to supplement iron in patients with ferropenia but without anaemia may depend on the clinical scenario and the patient's preference. The arguments for treating isolated ferropenia are based on the fact that iron is essential for all cells of the body. Symptoms of iron deficiency may occur without anaemia. Specifically, reduced physical performance and cognitive function, fatigue, headache, sleeping disorders, loss of libido, or restless-legs syndrome may be present without blunt anaemia and may improve upon iron supplementation.[3,29,38,79–84] Also nail growth, skin defects, and mucosal regeneration can be affected.[2]

4.2.2. ECCO Anaemia Statement 3D

IBD-associated iron deficiency and anaemia recur frequently and fast, even after treatment with intravenous iron. Recurrence of iron deficiency is lower in patients with higher post-treatment ferritin levels [EL 2]

Anaemia seems to recur frequently and fast after intravenous iron therapy.[74] The speed of recurrence relates to the size of post-treatment iron stores [as reflected by serum ferritin].[74] 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. Accordingly, it was suggested that intravenous iron replacement might aim at ferritin levels of up to 400 µg/L.[74]

4.2.3. ECCO Anaemia Statement 3E

After successful treatment of iron deficiency anaemia with intravenous iron, re-treatment with intravenous iron should be initiated as soon as serum ferritin drops below 100 µg/L or hemoglobin below 12 or 13 g/dL [according to gender] [EL2]

As iron deficiency anaemia recurs frequently and fast, iron maintenance therapy may prevent anaemia recurrence. The FERGImain study evaluated whether ferric carboxymaltose can prevent anaemia in patients who had previously been successfully treated for IBD-associated anaemia.[40] FERGImain was a randomized, placebo-controlled trial including non-anemic patients who had completed FERGIcor.[36] Serum ferritin was assessed every 2 months and patients received 500 mg of ferric carboxymaltose when ferritin levels fell below 100 µg/L. Kaplan-Meier analysis of patients becoming anemic showed significantly lower rates in ferric carboxymaltose-treated compared with placebo-treated patients (27% vs 40%, hazard ratio 0.62 [95% CI, 0.38–1.00]). Since the separation of the Kaplan-Meier curves continued to increase until the end of the study period, a further benefit from ferric carboxymaltose is anticipated beyond 8 months.[40] Of note, gastrointestinal symptoms and flares of IBD were less frequent in the ferric carboxymaltose group, and adverse event rates were comparable between ferric carboxymaltose and placebo. Although the study was not powered to detect a treatment effect on quality of life, a positive trend in terms of improved physical characteristics was observed in favour of ferric carboxymaltose.[40] The FERGImain study demonstrates that ferric carboxymaltose prevents recurrence of anaemia in patients with IBD. In contrast to the traditional 'watch and wait' strategy, FERGImain introduces the novel 'proactive' concept. Cost analysis favours such a 'proactive' approach to anaemia management since the average annual healthcare costs are more than twice as high for anemic compared with non-anemic IBD patients [USD 19,113 vs USD 7678].[85]

5. Management of Non-Iron Deficiency Anaemia

5.1. Classification of non-iron deficiency anaemia [NIDA]

5.1.1. ECCO Anaemia Statement 4A

The characterization of non-iron deficiency anaemia [NIDA] by MCV and reticulocytes is recommended [EL 5]

The WHO criteria for the hemoglobin cut-off are widely accepted and should be used also for NIDA. Modulating factors like pregnancy, high altitude, and age must be considered. Anaemia in IBD may have multiple causes besides iron deficiency. The causes of NIDA in IBD are indifferent to other conditions and thus can be classified according to MCV and reticulocytes [Table 2].[2,25,86,87] The initial work-up of anaemia should follow the algorithm in Figure 1. The general classification of anaemia is shown in Table 2.

It is not infrequent that more than one cause of anaemia exists in a particular patient.[3] NIDA may precede the initial diagnosis of IBD.[88] The risk of developing anaemia relates to disease activity, because both blood loss and anaemia of chronic disease are triggered by intestinal inflammation. For differential diagnosis it should be emphasized that the causes of NIDA in IBD can be common, occasional, or exceptional [Table 4].

Table 4. Causes of non-iron deficiency anaemia in IBD; adapted from reference[25].

Common	Anaemia of chronic disease
Occasional	Cobalamin deficiency
	Folate deficiency
	Drug-induced [sulphasalazine, 5-ASA, 6-MP, azathioprine]
Exceptional	Hemolysis
	Myelodysplastic syndrome
	Aplastic anaemia
	Glucose-6-phosphate dehydrogenase deficiency

Abbreviations: 5-ASA, 5-aminosalicylic acid; 6-MP, 6-mercaptopurine.

Anaemia of chronic disease [ACD] is the most frequent anaemia in hospitalized patients and develops in subjects suffering from diseases that are associated with chronic activation of cell-mediated immunity, such as chronic infections, immune-mediated inflammatory disorders, or malignancy. ACD is characterized by a normal or low MCV and low or normal reticulocyte counts. Of special clinical importance are also causes of NIDA related to IBD therapy,[89–91] to aplasia,[92,93] to autoimmune hemolysis,[94–99] and to B_{12} or folic acid deficiencies. Treatment of NIDA may include adjustment of IBD treatment, nutritional supplements [B_{12}, folic acid], treatment of other underlying causes of such as infections, inflammations or malignancies, use of erythropoiesis-stimulating agents [ESA] and, in exceptional cases, individualized approaches such as colectomy, splenectomy, or kidney [for secondary hyperoxaluria] or bone marrow transplantation.

5.2. Initiation of erythropoiesis-stimulating agents

5.2.1. ECCO Anaemia Statement 4B

Patients with anaemia of chronic disease with an insufficient response to intravenous iron and despite optimized IBD therapy may be considered for ESA treatment [EL 1] with a target hemoglobin level not above 12 g/dL [EL 5]

The presence of anaemia of chronic disease is a clear indicator of active disease. Therefore optimization of IBD treatment should precede any ESA treatment. In two large, randomized, placebo-controlled trials examining the effect of infliximab on hemoglobin levels, physical function, and fatigue in patients with ankylosing spondylitis or rheumatoid arthritis, it was demonstrated that infliximab treatment significantly improved hemoglobin levels compared with placebo even after adjusting for disease activity.[100,101]

In IBD patients requiring anti-tumor necrosis factor [TNF] treatment, response to therapy has been shown to improve erythropoiesis[102] by significantly increasing serum EPO and sTFR levels.[103] Of interest, infliximab has been the only way to treat anaemia in some IBD cases.[95,104] As anaemia of chronic disease probably results from decreased erythropoiesis secondary to increased levels of proinflammatory cytokines [such as TNF], anti-TNF may improve bone marrow output. It is likely, however, that the healing of ulcerated mucosa rather than its anti-TNF effects on the bone marrow triggers the good outcome.[87]

The erythroid response to intravenous [IV] iron can be checked by reticulocyte counts after iron infusions. Patients with a diagnosis of anaemia of chronic disease, whose anaemia does not, or only partially responds to anti-TNF and IV iron, may be considered for ESA treatment. Several studies indicate that a majority of patients with IBD respond to ESA treatment with an increase in hemoglobin and improvement of quality of life.[45,46,51,105] 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. There is no long-term ESA study in IBD, therefore the same caution measures apply. Concomitant IV iron should prevent functional iron deficiency and ferritin levels should be above 200 µg/L. Low transferrin and low EPO levels are associated with inadequate response to IV iron and may be used for selection of patients.[39]

5.3. Nutrition elements and vitamin supplementation

5.3.1. ECCO Anaemia Statement 4C

Deficiencies of Vitamin B_{12} and folate should be treated to avoid anaemia [EL 5]

Cobalamin and folate deficiency may occur in IBD, especially after ileal resection. Folate and cobalamin deficiency give rise to macrocytosis, and serum levels should be measured in patients with high MCV. In doubtful cases, measurement of homocysteine or methyl malonate can be performed. Increased homocysteine indicates tissue deficiency of either B_{12} or folate with a greater sensitivity than serum B_{12} measurement. Methyl malonate is specific for B_{12} deficiency and likewise has a better sensitivity.[106–108] Serum levels of vitamin B_{12} and folic acid should be measured at least annually, or if macrocytosis is present. Patients at risk for vitamin B_{12} or folic acid deficiency [eg small bowel disease or resection] need closer surveillance. The recommended timelines are based on expert opinions and reflect common clinical practice, but do not apply to patients with extensive small bowel resection, extensive ileal Crohn's disease, or ileal-anal pouch.[7]

Some commonly used drugs may affect erythropoiesis, both indirectly such as the 'antifolic' effect of salazopyrine [by inhibiting folate absorption] and directly as in the case of azathioprine or 6-mercaptopurine. Apart from folate deficiency, sulphasalazine or 5-aminosalicylic acid have been related to a minor degree of hemolysis or aplasia.[91,109,110]

5.4. Blood transfusions

5.4.1. ECCO Anaemia Statement 4D

In the treatment of anaemia, red blood cell transfusion may be considered when hemoglobin concentration is below 7 g/dL, or above if symptoms or particular risk factors are present [EL 4]. Blood transfusions should be followed by subsequent intravenous iron supplementation [EL 4]

In the past, transfusions of red blood cells were common in the treatment of anaemia in IBD. Such transfusion requirements vanished with the introduction of IV iron and ESA. Current policies restrict transfusions to special situations, such as anaemia with hemodynamic instability, severe acute anaemia, and/or failure of all other treatments.[111–113] The trigger to transfuse is variable between physicians and hospitals.

The decision to administer blood transfusions is not solely based on the hemoglobin level, but takes comorbidity and symptoms into account. To what extent blood transfusions affect immune function and whether they are cause-effectively linked to mortality in patients undergoing surgery or being treated in intensive care units, remains controversial.[84,107,114,115] Blood transfusions are widely used as an immediate intervention for rapid correction of severe or life-threatening anaemia. However, transfusions do not correct the underlying pathology and have no lasting effect. Other options [including IV iron with or without ESA] should be considered ahead of and after transfusions as these are only a transient fix which does not sustain normal hemoglobin.

5.5. Investigation of anaemia in IBD patients with comorbidities

5.5.1. ECCO Anaemia Statement 4E

Management of NIDA in IBD should always exclude other possible concomitant diseases such as infections, malignancie, and side effects of medications [EL5]

Patients with unexplained NIDA or/and characteristics of new-onset anaemia of chronic disease should always be also evaluated for the possibility of an underlying concomitant infection. Investigation may be guided by patient symptoms and may be based on clinical history, physical examination, and laboratory tests. In addition, intestinal or extraintestinal cancers with anaemia may complicate the course of IBD.[116] Thiopurines produce macrocytosis and may cause mild anaemia.[117]

5.6. Adjustment and optimization of IBD therapy

5.6.1. ECCO Anaemia Statement 4F

In case of ananaemia of chronic disease, treatment of IBD should be optimized in combination with anaemia-specific treatment [EL4]

In active IBD, inflammatory mediators may alter iron metabolism, erythropoiesis, and erythrocyte survival leading to the so-called anaemia of chronic disease. To manage this type of anaemia, the most important step is to induce complete remission.[99,118] Since disease activity is not always associated with an increase in acute phase proteins and may not be accompanied by clinical symptoms, endoscopy may be also needed to evaluate disease activity in patients with a low CRP.[5,7,21,25,87]

5.6.2. ECCO Anaemia Statement 4G

Thiopurines rarely cause isolated anaemia. If other causes of anaemia are excluded, the dose should be adjusted or discontinuation of therapy should be considered [EL4]

Azathioprine [AZA] and 6-mercaptopurine are effective drugs for inflammatory bowel disease [IBD] but they are associated with a number of side effects. The incidence of AZA-related adverse events ranges from 5% to 25%, and bone marrow toxicity is one of the most serious event.[119] In fact, AZA has been associated with pancytopenia, autoimmune hemolytic anaemia, leukopenia, thrombocytopenia, macrocytosis, and pure red cell aplasia.[120–123] Retrospective studies[124–126] have reported an overall frequency of leukopenia in 3.2%. Leukopenia occurs when 6-thioguanine [6-TG] accumulates in tissues, including bone marrow tissue.[8] The thiopurine methyltransferase [TPMT] genotype and enzyme activity cannot explain the majority of cases with leukopenia.[124] In a study with 41 Crohn's disease patients developing leukopenia or thrombocytopenia during AZA/6-MP, treatment only 27% of cases could be explained by these most frequent TPMT variants.[127] In addition, TPMT enzyme activity measurement is not always predictive and is influenced by drug interactions and blood transfusion.[128] Some cases can be explained by the presence of rare TPMT variants.[129,130] In others cases an increased TPMT-6-TG route activity may result from administration of sulfasalazine, mesalamine, allopurinol, cotrimoxazole, or diuretics.[131,132]

Conflict of Interest

ECCO has diligently maintained a disclosure policy of potential conflicts of interests [CoI]. The conflict of interest declaration is based on a form used by the International Committee of Medical Journal Editors [ICMJE]. The CoI statement is not only stored at the ECCO Office and the editorial office of JCC but also is open to public scrutiny on the ECCO website [https://www.ecco-ibd.eu/about-ecco/ecco-disclosures.html] providing a comprehensive overview of potential conflicts of interest of authors.

The ECCO Consensus Guidelines are based on an international Consensus process. Any treatment decisions are a matter for the individual clinician and should not be based exclusively on the content of the ECCO Consensus Guidelines. The European Crohn's and Colitis Organisation and/or any of its staff members and/or any consensus contributor may not be held liable for any information published in good faith in the ECCO Consensus Guidelines.

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