Anemia in Inflammatory Bowel Disease: A Neglected Issue in Comprehensive Inflammatory Bowel Disease Management

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ABSTRAK

Anemia merupakan komplikasi ekstraintestinal tersering dari inflammatory bowel disease (IBD) dan berkorelasi signifikan dengan berbagai keluaran penyakit yang lebih buruk seperti angka rawat inap, angka relaps, kebutuhan tindakan pembedahan yang lebih tinggi, dan kualitas hidup yang lebih rendah. Prevalensi anemia pada pasien IBD dilaporkan bervariasi, akan tetapi diperkirakan berkisar antara 8,8% hingga 74%. Meskipun tingginya prevalensi tersebut, hingga saat ini masih terdapat kesenjangan antara protokol skrining dan pengobatan anemia pada praktik klinis sehari-hari. Sehingga dapat disimpulkan bahwa anemia pada IBD merupakan suatu komplikasi IBD yang bersifat signifikan dan perlu ditatalaksana secara komprehensif namun seringkali dikesampingkan. Anemia pada IBD dapat disebabkan oleh berbagai faktor, dengan anemia defisiensi besi sebagai etiologi tersering. Manajemen komprehensif anemia pada IBD mencakup skrining aktif, evaluasi dari etiologi, tatalaksana holistik, dan monitoring. Optimalisasi terapi IBD juga merupakan hal penting karena akan berkontribusi pada perbaikan kondisi anemia. Pendekatan dan kolaborasi multidisiplin diperlukan untuk memberikan pelayanan pasien IBD dengan lebih baik.

Kata kunci: *Anemia, inflammatory bowel disease, kolitis ulseratif, penyakit crohn.*

ABSTRACT

Anemia is the most common extraintestinal inflammatory bowel disease (IBD) manifestations and is significantly correlated with several adverse impacts such as higher hospitalization rate, relapse rate, surgical intervention requirement, and low quality of life. The prevalence of anemia in IBD patients is greatly varied between reports, with an estimated prevalence of 8.8% to 74%. However, studies showed there were still gaps in the screening protocol and anemia treatment in daily practice. Anemia in IBD tends to be an overlooked complication of significance and must be adequately addressed. Anemia in IBD may be caused by interplay of

several factors, with iron deficiency anemia being the most common etiology. Comprehensive management of anemia in IBD should consist of active screening, evaluation of the etiology, holistic treatment, and follow-up monitoring. Optimization of IBD therapy should be emphasized because it also may improve the anemic condition. A multidisciplinary approach and collaboration are needed to ensure better IBD care.

Keywords: *Anemia, inflammatory bowel disease, ulcerative colitis, Crohn disease.*

INTRODUCTION

Inflammatory bowel disease (IBD), which consists of ulcerative colitis (UC) and Crohn's Disease (CD), is characterized by chronic inflammation of the gastrointestinal tract. Pathogenesis of IBD is multifactorial and is generally thought of as an interaction of genetic, environmental, host immunological factors, and intestinal microbiota.[1] Prolonged inflammation in IBD patients may cause several intestinal and extraintestinal complications, with anemia being the most common extraintestinal complication. Anemia in IBD patients can be caused by complex interactions of all factors such as iron deficiency, persistent inflammation, blood loss due to gastrointestinal bleeding during IBD flare, folate and vitamin B12 deficiency, and the side effects of drugs. Therefore, a complete evaluation and stepwise diagnostic approach of anemia in IBD should be implemented, as many factors may interplay as the cause of anemia.[2] Many studies showed the significant impact of anemia on decreased quality of life of IBD patients. Anemia is also associated with higher rates of hospitalization and prolonged hospital length of stay.[3] While practitioners generally recognize the significant adverse impact of anemia in IBD; a study showed there were still gaps in the screening protocol and anemia treatment in daily practice.[3,4] Therefore, anemia in IBD tends to be an overlooked yet significant complication which needs to be adequately addressed.[3]

THE BURDEN OF ANEMIA IN IBD PATIENTS

The prevalence of anemia in IBD patients is greatly varied between reports. Anemia is recognized as the most common extraintestinal manifestation of IBD.[5] The prevalence was estimated to be between 8.8 to as high as 74%; it greatly depends on subgroup IBD patients being studied. A study in a Brazil outpatient clinic consisting of 100 UC patients and 100 CD patients reported the prevalence of anemia of 21%. They found no significant difference between the anemia prevalence of UC and CD patients (18% vs. 24%). Iron deficiency anemia (IDA) being the most common etiology of anemia (6% in UC and 10% in CD), followed by anemia of chronic disease (ACD), which represented 6% of both groups.[4] A large five-year cohort study in the United States involving 1821 IBD patients (1077 CD, 744 UC) showed that the prevalence of anemia was 50.1% (CD: 53.3% vs. UC 44.7%). Several risk factors were analyzed, which showed that disease severity was closely related to anemia.[6] Meta-analysis by Filmann et al.[7] in 2014 revealed that the prevalence of anemia in IBD cases in Europe to be 27% in the CD group and 21% in the UC group. Further analysis showed that anemia was associated with the usage of IBD-specific medications and disease activity status. Patients who were treated with IBD-specific drugs (odds ratio 1.54) and patients with active disease (odds ratio 2.72) were more likely to have anemia. This meta-analysis also showed that UC patients were less likely to experience anemia than CD patients (odds ratio 0.77). Assessment of iron status among anemic patients revealed that more than 50% were iron deficient.

A large multicenter study (ECCO-EPICOM study) evaluating 1871 newly diagnosed patients, including 686 CD patients, 1021 UC patients, and 164 unclassified IBD did follow up monitoring for one year. The prevalence of anemia at diagnosis was higher among CD patients than UC patients (44% vs. 31%) in Western European countries. During one-year follow-up, they found that 49% of CD and 39% of UC patients experienced at least one episode of anemia. Further analysis regarding the type of anemia found IDA approximately 12-17%, ACD

10-27%, and mixed causes in 23-31%.[8]

A study done in an Asian country, namely India, showed that anemia was found in more than half of UC patients even in clinical remission, with IDA being the most common finding.[9] Another long-term cohort study of IBD patients in Turkey showed that anemia was detected in 548 (58.2%) patients, from the total of 941 IBD patients. They also found that anemia was more prevalent among female and CD patients. Age of the IBD disease was highly correlated with anemia, with an incidence rate calculated as 103.45 per 1,000 patient-years. This finding showed that anemia incidence in IBD might present upon presentation and correlated with the IBD disease course.[10]

IMPACT OF ANEMIA IN IBD PATIENTS

Many studies showed that anemia significantly affects patients' quality of life and may be associated with a more severe IBD course. Anemia may affect the productivity of patients due to fatigue, affecting emotional and also cognitive functioning. Anemia in IBD is also implicated with more healthcare resources utilization and higher medical cost burden.[11] A study showed that anemia therapy might lead to quality of life (QOL) improvement in IBD patients.[12]

A five-year-longitudinal analysis performed by Koutroubakis et al. involving 410 IBD patients (245 CD, 165 UC) showed that the prevalence of anemia was 37.1%, and IBD patients with anemia required more health care, had lower QOL, and was associated with more severe disease activity. Further analysis also showed that persistent or recurrent anemia for three or more years was significantly associated with more frequent hospitalizations, health care related visits, and surgeries for IBD.[6] Therefore, more aggressive management of anemia in IBD patients should be emphasized. Analysis of 15,761 patients IBD by Michailidou et al. found that more than half were having anemia, and anemia was strongly correlated with increased risk for an emergency operation and sepsis. Anemia was also served as a predictor for severe morbidity and increased length of stay.[13]

PATHOPHYSIOLOGY

Anemia in IBD may result from multiple factors, with iron deficiency becoming the most common cause.[4] Interplay of multiple factors may occur, such as iron deficiency, vitamin deficiency, chronic inflammation, diet, micronutrient malabsorption, surgical history, disease activity, medications being used, IBD location and duration, and gastrointestinal bleeding (either visible or occult bleeding). Many journals stated that anemia in IBD is a model of combination between iron deficiency and chronic inflammation.[2]

Iron Deficiency Anemia in IBD

Iron deficiency anemia may be caused by absolute or functional iron deficiency. Absolute iron deficiency is defined as severely reduced or absence of iron stores in the body. Functional iron deficiency state is defined as adequate body iron stores but insufficient iron availability for incorporation into erythroid precursors; these findings are commonly caused by elevated hepcidin levels.[14] Dietary iron is absorbed mainly in the duodenum and proximal jejunum, with approximately 2 mg of iron absorbed daily. Approximately 1-2 mg iron daily is mainly lost from skin desquamation, shedding of intestinal epithelial cells, and blood loss. Absorbed iron will be bound to transferrin, an iron transport protein, transported in circulation and delivered to bone marrow as primary resources for erythropoiesis. Old red blood cells will be phagocytized by macrophages and recycled for new red blood cells. Excess iron will be bound to a storage protein called apoferritin, forming ferritin.[15,16] Hepcidin also plays significant roles in systemic iron regulation. High hepcidin levels may inhibit intestinal iron absorption, macrophage iron recycling and inhibit erythropoiesis.[17] The iron deficiency state in IBD patients may be caused by chronic gastrointestinal bleeding or blood loss during IBD flare episodes, therefore contributing to negative iron balance. Inflammation lesion located at duodenum or proximal jejunum caused by CD may contribute to further iron absorption impairment. Also notably, strict dietary restrictions may also contribute to the development of iron deficiency anemia due

to low intake. Iron metabolism may also be impaired in chronic inflammation state due to the IBD condition. Elevated proinflammatory cytokines may impair the transportation of iron for erythropoiesis from iron stores to bone marrow, which is reflected in adequate ferritin levels but low transferrin saturation levels.[16,18]

Anemia of Chronic Disease in IBD

IBD condition resulting in chronic inflammation state does not only occur locally in the intestinal mucosal but also as chronic systemic inflammation. A study showed that IBD patients had elevated circulating levels of proinflammatory cytokines and chemokines also related to local intestinal inflammation and tissue damage.[19] A study from Antunes et al. showed that higher C-reactive level protein (CRP) levels were found among anemic IBD patients and increased CRP by each 1 mg/L increased the risk for anemia.[4] Elevated inflammatory cytokines may result in the suppression of erythropoiesis. Interleukin 1 (IL-1) and Tumor Necrosis Factor (TNF) inhibit the response of bone marrow to anemia by reducing erythropoietin production. Interleukin 6 (IL-6) increased hepcidin production, therefore inhibiting the iron absorption and transportation of iron from iron storage.[17,18,20] Chronic inflammatory conditions also shorten erythrocyte survival, which is mainly caused by increased activation of macrophage and increased erythrocyte destruction rate in the reticuloendothelial system.[20]

Erythropoietin and IBD

Erythropoietin (EPO), the primary regulator of erythropoiesis, a hormone secreted by the kidney, has blunted response in chronic inflammatory conditions such as IBD. Inflammatory cytokines also may impair the production of EPO. Some studies showed higher EPO levels among IBD patients, possibly due to part of the compensation to the anemic condition. However, the elevated production may still be inadequate according to anemia condition, which is termed relative EPO deficiency.[21] The role of EPO stimulating agent (ESA) usage in anemia IBD management may be beneficial when IBD patients had been adequately repleted but still had anemia, possibly due to EPO deficiency. ESA was used to overcome this problem.[22]

IBD Drug-induced Anemia

Common IBD medications such as sulfasalazine, azathioprine, or 6-mercaptopurine have a side effect of myelosuppression which manifests as anemia, leucopenia, thrombocytopenia, or pancytopenia. The incidence of bone marrow suppression due to thiopurines and azathioprine are reported ranging from 2-5% and 2-4%, respectively.[23]

Micronutrient Deficiency and Anemia

Patients with IBD are at higher risk for malnutrition and especially micronutrient deficiency. This condition may be related to the malabsorptive condition caused by IBD, persistent inflammation, chronic gastrointestinal bleeding post-surgery, and decreased oral intake. Deficiency of iron, folate, and vitamin B12 may also lead to anemia. A study by Park et al.[24] showed that 39% of IBD patients had either folate, vitamin B12, or 25-OH-vitamin D deficiency.Study by Huang et al.[25] showed the prevalence of vitamin B12 deficiency was 14.9% and folate deficiency was 13.3%. Vitamin B12 and Folate deficiency may lead to the development of macrocytic Anemia.

DIAGNOSTIC APPROACH

The basic understanding of interpreting laboratory results of anemia workup is essential for diagnosing anemia in IBD. Sometimes, it may be challenging to determine the actual cause of anemia in IBD due to overlapping anemia mechanisms and contributing factors.[26]

World Health Organization (WHO) defined the hemoglobin (Hb) cut-off for Anemia in the general population as lower than 12 g/dl for women, lower than 11 g/dl for pregnant women, and lower than 13 g/dl for men. Several studies and consensus by European Crohn's and Colitis Organisation (ECCO) used the same Hb cut-off for anemia diagnosis in IBD.[27]

ECCO recommended anemia workup should be commenced whenever hemoglobin level was below normal. History taking should be done carefully, consisting of questions regarding the history of disease activity, recent gastrointestinal bleeding, medication being taken, dietary

history, anemia symptoms, occupation, travel and family history, menstruation cycle, alcohol consumption, history of bleeding disorders, or excessive bruising, and surgical history. A comprehensive physical examination is warranted to find the sign of anemia, bleeding disorder, organomegaly, and tumor.[27,28]

ECCO differentiated anemia laboratory workup into two categories, basic and extensive workup. Basic workup was determined as the minimum examination in order to evaluate the cause of anemia in IBD. Minimum workup includes Hb, red blood cell count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC), reticulocytes count/production index, red cell distribution width (RDW), different blood cell count, serum ferritin, transferrin saturation, CRP concentration, reticulocyte count, thrombocyte count, and leucocyte count. Extensive workup is warranted to further determine the cause of IBD anemia after basic examination, including 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. ECCO recommended having hematological consultation if the cause of anemia is still unknown despite extensive workup.[27]

Interpretation of anemia laboratory workup result may begin from the interpretation of MCV and MCH to categorize the type of Anemia into microcytic/normocytic/macrocytic anemia. A common anemia diagnosis algorithm may be applied in evaluating anemia in IBD (**Figure 1**). Microcytic anemia in IBD may have resulted from iron deficiency and chronic disease. Normocytic anemia may have resulted from chronic disease or other hematological disorders. Macrocytic anemia may be related to folate acid and vitamin B12 deficiency due to malabsorption or strict dietary restriction, IBD drugs usage such as azathioprine, 6-mercaptopurine, sulfasalazine.[27]

Reticulocyte count may represent the erythropoiesis compensation response due to low Hb level. Low reticulocyte count may indicate inappropriate erythropoiesis condition, which occurred in IDA whilst high reticulocyte count may be related to the hemolytic process. Reticulocyte production index (RPI) is more useful than absolute reticulocyte count. RPI can easily be calculated using the formula: Reticulocyte percent x Hematocrit/45 x 1/ correction factor.[26,29] RDW is reflecting the broadness of erythrocyte size distribution or anisocytosis.[30] High RDW value is found among patients with IDA.[31] Disease activity and inflammation degree in IBD related to CRP level. High CRP levels may indicating ongoing inflammation process that may inhibit the erythropoiesis in IBD patients.[4] Platelet and white blood cell count is helpful to determine whether the anemia was part of pancytopenia or not. Pancytopenia may be caused by bone marrow failures such as aplastic anemia, myelodysplastic anemia, or other hematological malignancies.[32]

Iron Studies

Iron studies are mandatory for evaluating the iron status of anemic IBD patients, which is most commonly caused by iron deficiency. Ferritin is a laboratory examination to evaluate body iron storage. While low ferritin serum level is a marker of functional iron deficiency, ferritin is also categorized as an acute phase reactant protein, which may be elevated in inflammatory conditions such as IBD. Therefore, interpretation of ferritin should be made carefully, as the measured serum ferritin in inflammatory conditions may not be well correlated with the actual iron storage condition.[26,33] ECCO recommended using ferritin cut-off level of 30 μg/L to be used in diagnosing iron deficiency anemia in IBD and using the cut-off level of 100 μg/L if the IBD patients are in an active inflammatory condition.[27] Transferrin is a glycosylated protein that functions as a transport for iron to the usage and storage sites. Transferrin saturation (TSAT) is reflecting the percentage of binding sites on all transferrin molecules occupied with iron molecules. TSAT is simply calculated by dividing iron serum with total iron-binding capacity (TIBD). A low level of TSAT is consistent with the iron deficiency condition. Therefore, TSAT is a helpful marker for the diagnosis of IDA. However, transferrin may be

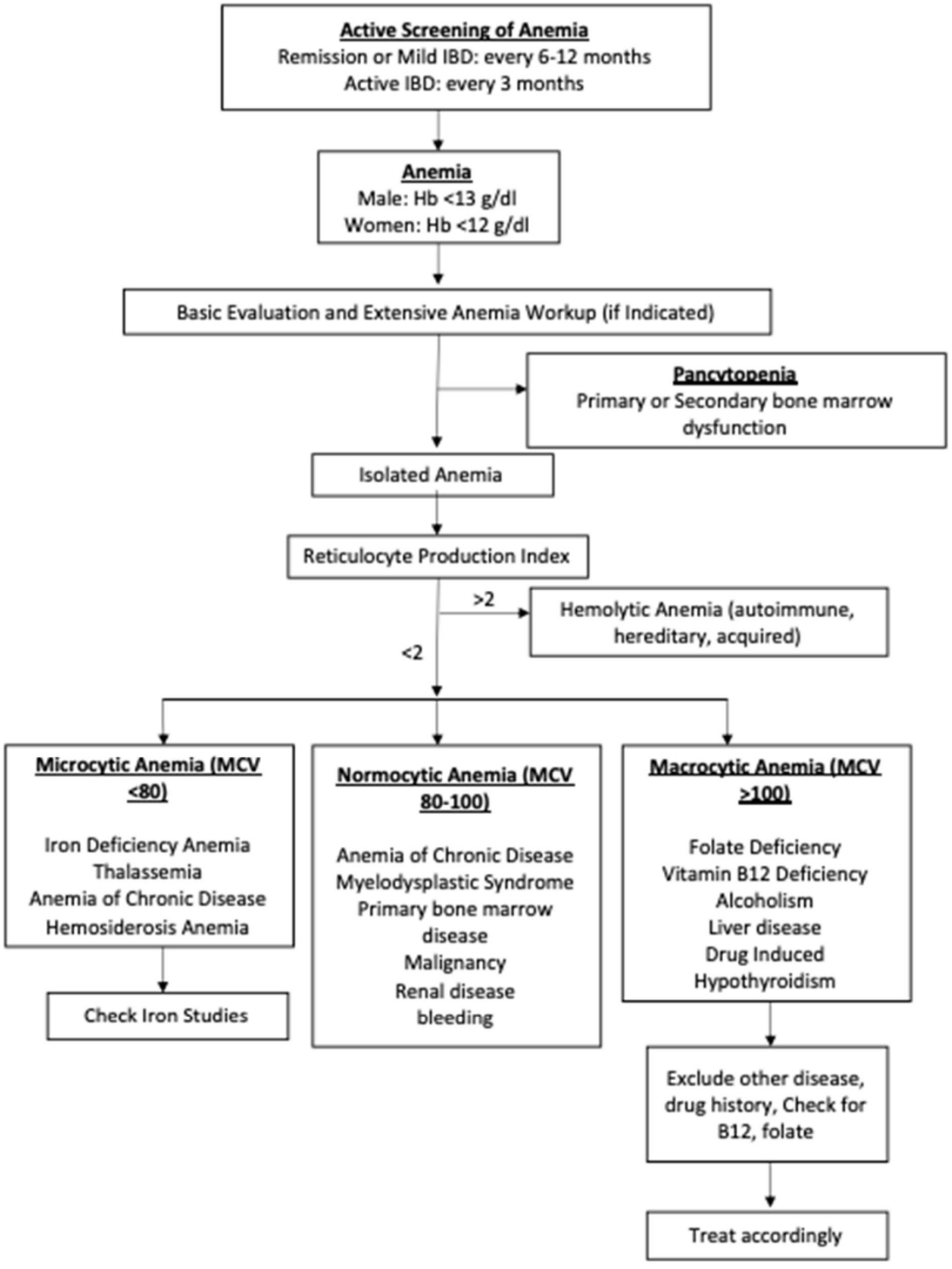

Figure 1. Approach to Anemia Screening and Evaluation in IBD patients[26,27,32]

downregulated in inflammation conditions.[26,34] Soluble transferrin receptors (sTfR), a novel biomarker for iron studies, is found to be unaffected by inflammation condition or concomitant chronic disease. Therefore, it may serve to be a valuable diagnostic tools to differentiate iron deficiency and chronic disease anemia, especially IBD. Further studies are needed to validate the reference range in IBD.[31,35,36]

According to ECCO in their European Consensus on the Diagnosis and Management of

Iron Deficiency and Anemia in IBD, diagnostic criteria for IDA should be differentiated according to the status of inflammation of IBD patients. In non-active IBD patients who are defined as having no active clinical symptoms (diarrhea, hematochezia), no active endoscopic inflammation lesions, and no elevation of inflammatory biochemical marker (CRP, WBC); serum ferritin <30 μg/L may be indicative for IDA. While serum ferritin < 100 μg/L cut-off should be used if there is active inflammation. Anemia of chronic disease in IBD can be diagnosed if there is biochemical or clinical evidence of active inflammation and ferritin level > 100 μg/L and TSAT < 20%. A ferritin level of 30-100 μg/L may indicate the presence of a combination between IDA and ACD.[26,27]

MANAGEMENT

Management of anemia in IBD patients should be comprehensive and targeted to the underlying etiology, as outlined above. The stabilization of the IBD disease course, in conjunction with dietary regulation, should be optimized. All patients with IBD should be actively screened for anemia. Screening of anemia can be employed every 6-12 months for patients in remission and every three months in active IBD patients.[26]

Management of IDA

ECCO recommended that IDA should be treated with iron supplementation in all IBD patients. The goal of treatment should be normalization of the Hb value and restore iron stores. ECCO recommended Hb improvement should be at least 2 gr/dl within four weeks of treatment.[27]

Iron supplementation may be given orally or intravenously. ECCO recommends intravenous iron supplementation as the first-line treatment, especially in patients with active IBD, documented previous oral iron intolerance, Hb below 10 gr/dl, and patients in ESA therapy. However, in some developing countries, this recommendation may not be applicable due to the higher cost of the intravenous iron regimen, required administration by a healthcare professional, and required close monitoring due to the possibility for iron overload and anaphylactic reactions. Intravenous iron has some advantages over oral supplementation, especially in IBD patients, which is faster repletion of iron stores and effective even with impaired intestinal absorption. On the other hand, oral iron supplementation becomes a more feasible option for developing countries, as iron supplementation is inexpensive and can be self-administered by the patients at home. Several issues are related to the oral iron supplementation in IBD patients, which may create issues in attaining Hb goal and maintaining patient compliance, such as the impaired intestinal absorption and gastrointestinal side effects (abdominal pain, nausea, constipation).[27,28] Oral iron supplementation was also found to cause gut bacterial diversity shifting in IBD patients.[37] Real-world data from Germany, including more than 1000 IBD patients with IDA, showed that IBD patients who received intravenous iron supplementation had less hospitalization rate and lower total healthcare costs than patients receiving oral iron.[38] The safety and effectiveness of oral iron supplementation in IBD patients have been shown by several studies. Therefore, oral iron supplementation is still recommended by ECCO for inactive IBD, no history of previous oral iron intolerance, and patient with mild anemia (Hb 11.0-11.0 gr/dl for nonpregnant women and 11.0-12.9 gr/dl in men).[26,27] Several newer oral and intravenous iron supplementation have been developed in order to minimize gastrointestinal side effects and anaphylactic reaction. It is also noted that oral iron side effects are dose-dependent.[28] ECCO recommended no more than 100 mg elemental iron per day should be given in patients with IBD. Estimation of iron needs may be based on baseline Hb and body weight. For patients with Hb 10-13 gr/dl the estimated total iron need is 1000 mg and 1500 mg, respectively for bodyweight <70 kg and ≥70 kg. For patients with Hb 7-10 gr/dl and body weight < 70 kg required 1500 mg total iron, while patients with similar Hb and body weight ≥70 kg required 2000 mg.[27,39] List of oral and intravenous iron supplementation can be seen in **Table 1**.[28,40]

Blood transfusion is generally not

Table 1. List of Oral and Intravenous Iron Preparations[28,40]

Preparations	Elemental iron (mg)	Dose
Oral		
Ferrous Sulfate	65	325 mg tid
Ferrous Gluconate	36	300 mg tid
Ferrous Fumarate	33	100 mg tid
Iron Polysaccharide Complex	150	150 mg tid
Carbonyl iron	50	50 mg bid
Intravenous		
Iron Sucrose		100-200 mg over 2-5 minutes OR infusion over 15 minutes
Iron Dextran		100 mg over 2 minutes
Ferric Gluconate		125 mg over 10 minutes
Ferumoxytol		510 mg over 15 minutes
Sodium Ferric Gluconate Complex		62.5-125 mg over 1 hour
Ferric Carboxymaltose		750 mg over 15 minutes

recommended for first-line treatment of IDA due to several possible side effects. A blood transfusion may be given for patients with active bleeding with unstable hemodynamics, critical anemia (Hb <7 gr/dl), having significant cardiovascular comorbidity, which warrants a higher hemoglobin level. Packed red cell transfusion should be considered as temporary management only in iron deficiency anemia management. The hemoglobin threshold for initiating blood transfusion may vary between healthcare facilities.[26, 28,41]

ESA usage in managing anemia in IBD still require further studies. The non-optimal response of Hb normalization after iron correction therapy may indicate concurrent ACD. ESA should be given after restoration of iron level. Possible risks of ESA administration in IBD patients are the risk of venous thromboembolism and the possibility of the response of EPO receptors that may be expressed in several malignant cells.[26] ECCO recommended ESA initiation for patients with ACD with an insufficient response to iron correction and after optimization of IBD therapy. Hemoglobin target with ESA therapy should not higher than 12 g/dl.[27]

Monitoring of IDA treatment should be performed every three months for at least a year after correction and periodically 6 and 12 months after. Recurrent anemia after correction warrants further evaluation as it may indicate persistent intestinal disease activity. Maintenance therapy may be needed in order to maintain the adequacy of iron stores and Hb. Iron supplementation can be resumed if the ferritin level was lower than 100 μg/L.[26,28] Summary of IDA management in IBD patients can be seen in **Figure 2**.

Management of Non-Iron Deficiency Anemia

Dietary supplementation with cobalamin and folic acid should be given to correct whenever folate and vitamin B12 deficiency is present. Correction of malnutrition may be needed. Guidelines from The Asian Working Group regarding diet and inflammatory bowel disease, published in 2019 or practical guidance of clinical nutrition in IBD by the European Society for Clinical Nutrition and Metabolism, may be used as dietary guidance.[42,43] Optimization of IBD treatment in order to reduce inflammation or to achieve remission should be emphasized, as high inflammatory cytokines level may inhibit erythropoiesis, leading to refractory ACD. Drug-induced Anemia such as azathioprine and 6-mercaptopurine may be managed by switching to other drugs if possible or to have the dose adjusted. Cooperation with a hematologist may be required in managing anemia in IBD. Other causes of non-iron deficiency anemia should be evaluated and excluded, such as infections and malignancies, and managed concomitantly.[27]

CONCLUSION

Anemia in IBD is often a neglected health issue in IBD management. Anemia in IBD is highly correlated with a worse prognosis and lower quality of life. Active screening of anemia

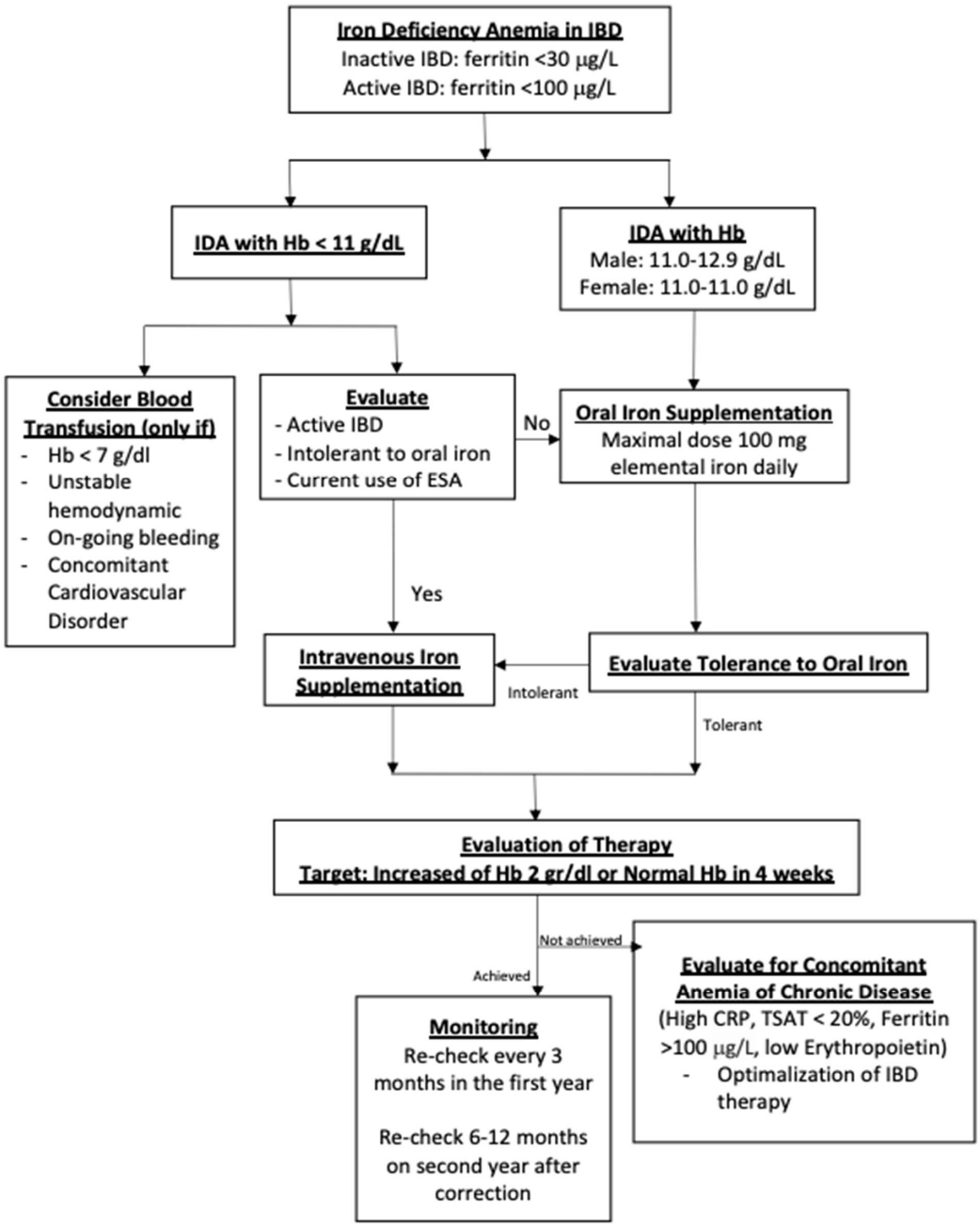

Figure 2. Management of Iron Deficiency Anemia in IBD Patients[26,27]

in IBD, structured evaluation, comprehensive management, and multidisciplinary collaboration are needed.

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