doi.org/10.58931/cibdt.2024.2335

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MANAGEMENT OF ANEMIA IN INFLAMMATORY BOWEL DISEASE

Introduction

Anemia is one of the most common complications of inflammatory bowel disease (IBD), with estimates of its prevalence varying from 9-74%.[1] It is estimated to affect more than 1.2 billion people worldwide and evidence suggests that the incidence of anemia in people with IBD is almost double that of people without IBD (92.75 people with IBD per 1000 person-years vs 51.18 without IBD per 1000 person-years).[2,3] Having a thorough approach to anemia in IBD is important because it is common and potentially dangerous, and because of its potential to arise from multiple different pathological and/or physiological processes.

Definitions

The parameters by which we define anemia are somewhat arbitrary because they are defined more by deviation from the mean rather than by clinical effects. Most laboratories report normal reference values that are sometimes modified to reflect average differences in age and sex. Other factors such as ethnicity or living at higher altitudes are sometimes considered; as a result, normal values can therefore vary from institution to institution. The normal values are not different for patients with IBD.

The normal values for measures of hemoglobin (HGB) concentration have changed over time but remain near the original cutoffs of 130 g/L in men and 120 g/L in women. Other red blood cell (RBC) indices that may be useful include the mean corpuscular volume (MCV) and the reticulocyte distribution width (RDW). The normal MCV is considered to be between 80-100 fL, however, the normal values for RDW are not well-defined.[4] Total body iron stores are considered to be low when serum ferritin levels are 30 mg/L or below.[3]

Evaluation

The management of anemia in IBD is dependent on establishing all underlying causes. With so many potential underlying and interconnected causes for anemia, having a structured approach can help avoid missing a contributing factor. Several conceptual approaches exist, with one of the most common consisting of considering causes that result in macrocytic, microcytic, or normocytic RBCs (the "morphological approach"). This narrows down the most common etiologies for macrocytosis and microcytosis, although the differential diagnosis for normocytic anemia remains large, and each category encompasses unrelated etiologies. Perhaps a more physiology-based conceptual structure, the "kinetic approach," involves categorizing causes of anemia as resulting from decreased production of erythrocytes, increased destruction of erythrocytes, and destruction of erythrocytes.[5] A list of some causes for anemia are provided in **Table 1**, with the etiologies of particular concern in IBD shown in bold font. It is worth noting that these etiologies can be related or independent of each other. Gastrointestinal (GI) malignancy can cause bleeding but can also cause anemia of inflammation. A patient with active IBD can also have medication- or infection-related anemia. The clinician should also consider artifactual anemia, i.e., adequate HGB concentration diluted by physiological processes such as pregnancy or iatrogenic processes such as intravenous fluid resuscitation.

Abnormal Production	Increased Destruction	Increased Loss
Chronic Inflammation • **Active IBD** • **Extraintestinal manifestations** • **Other IMIDs†** • Chronic heart failure • COPD • Chronic kidney disease Metabolic Disease • Hypothyroidism • Adrenal insufficiency Nutrient deficiency • **Iron** • **B12** • Folate Malabsorption • **Short gut syndrome** • Celiac • Bariatric surgery Bone Marrow disorders • Myelodysplasia • Aplastic anemia • Infection (HIV, hepatitis) • Infiltration	Mechanical • Artificial heart valve Hemolytic anemia • Acquired (immune, **medications**) • Inherited (hemoglobinopathies, G6PD deficiency, spherocytosis) Physiological • Hypersplenism o Cirrhosis o **Lymphoma**	GI blood loss • **Active IBD** • **Intestinal surgical anastomoses** • Peptic ulcer disease • **GI malignancy** • Angiodysplasia • GAVE • Ischemia Non-GI blood loss • Hematuria • Menorrhagia • Epistaxis • Blood donation

Table 1: Etiologies of anemia; *courtsey of Chris Sheasgreen, MD, FRCPC*
Abbreviations: COPD: chronic obstructive pulmonary disease; **G6PD:** glucose-6-phosphate dehydrogenase; **GAVE:** gastric antral vascular ectasia; **GI:** gastrointestinal; **HIV:** human immunodeficiency virus; **IBD:** inflammatory bowel disease; **IMIDs:** immune-mediated inflammatory diseases
Etiologies of particular concern in patients with IBD are in bold font.
† Immune-mediated inflammatory disease

Evaluation of anemia in IBD, as in all clinical situations, requires consideration of the individual patient's clinical context. It should begin with a thorough history with particular attention to major milestones in the IBD natural history such as surgeries and medication exposures. The history should include a review of symptoms with attention paid to common symptoms of severe anemia such as fatigue, shortness of breath, orthostatic dizziness, pallor, palpitations, and chest pain. Less dangerous complications such as rashes can provide clues to the underlying etiology.

A dietary review is crucial as many IBD patients have significant dietary restrictions. Patients may adopt these restrictions as a means of symptom control based on their own idiosyncratic reactions to foods in the past or because of perceived benefit for overall health and flare avoidance. There is insufficient data to comment on the risk of anemia or specific micronutrient deficiencies from these dietary strategies. Regardless, clinicians should remain aware that dietary restriction is common in IBD patients, may lead to micronutrient deficiencies, and has been associated with decreased quality of life.[6,7]

A review of medications is necessary as some can lead to anemia as well as morphological changes to the RBCs. These changes can provide clues to the etiology but can also confuse the situation in cases in which there are multiple contributing factors to the anemia. For example, methotrexate is an antifolate medication that can result in macrocytosis. This could offset microcytosis caused by iron deficiency. A list of anemia-associated medications common in IBD or the general population is provided in **Table 2.**

Assessment of clinical disease activity is paramount and can be imperfectly quantified by tools such as the Mayo score or the Harvey Bradshaw Index.[8] Particular attention should be dedicated to inquiring about GI blood loss such as hematochezia, melena, or even hematemesis. The gastroenterologist should not forget extraintestinal blood loss sources such as menorrhagia, epistaxis, and hematuria. Inpatient status can have diagnostic value because intravenous fluid administration for resuscitation can cause a dilutional effect on serum lab results.

More objective measures of disease activity include C reactive protein (not GI specific) and fecal calprotectin. Cross sectional imaging, including enterography or intestinal ultrasound, can provide promising and accessible assessments of IBD intestinal activity. Endoscopy (usually colonoscopy or flexible sigmoidoscopy, keeeping upper endoscopy in mind for patients with documented or possible upper GI

- Methotrexate (antifolate)
- Azathioprine (bone marrow suppression)
- Janus kinase inhibitors (erythropoiesis suppression)
- Mesalamine (bone marrow suppression)
- Antibiotics (autoimmune)
- Cyclosporine (autoimmune)
- Prednisone (autoimmune)
- TNF Inhibitors
- Risankizumab
- Ozanimod

Table 2: Medications (mechanisms) associated with anemia in inflammatory bowel disease; *courtsey of Chris Sheasgreen, MD, FRCPC*

Crohn's disease) allows assessment of disease activity as well as other sources of bleeding such as surgical anastomoses and malignancy.[8]

Two of the most important laboratory tests are the complete blood count (CBC) and iron studies. Regarding the CBC, take note of other cell lineages (pancytopenia might suggest a bone marrow disorder). As mentioned above, MCV can help steer the diagnosis toward certain etiologies (e.g., iron deficiency tends toward microcytosis whereas myelodysplasia, vitamin B12 and folate deficiency, and the drug effect from methotrexate and azathioprine can lead to macrocytosis). Remember that reticulocytes are larger than mature erythrocytes and can skew the MCV high.[9]

Iron deficiency is the most common cause of anemia in patients with IBD, therefore, interpreting serum iron stores is of paramount importance. However, a Scandinavian study has found that most causes of anemia were attributed to both iron deficiency and chronic inflammation.[10] In addition to serum ferritin as a marker of iron deficiency, transferrin saturation can be calculated to confirm that the body iron stores are low (<20%). However, in the context of anemia of chronic inflammation (usually normocytic), ferritin levels can be normal or high, but the transferrin saturation might still be low.[5] In these situations, a low transferrin saturation with a ferritin level as high as 100 mg/L might be considered to have iron deficiency. A trial of iron replacement in these patients could be considered diagnostic as well as therapeutic, rather than proceeding to bone marrow biopsy as gold standard for diagnosis.[17]

Vitamin B12 and folate deficiencies can lead to macrocytic anemias. However, in Canada, flour is fortified with folate, thus the rates of folate deficiency are below 1%.[11] Combined micronutrient deficiencies (or other factors such as the medication effect) could affect RBC morphology in opposite ways, resulting in normocytosis.[9] Some studies have shown an association between low levels of zinc and copper with anemia. Therefore, these micronutrients could be considered as part of an extended workup in this population at risk for micronutrient deficiencies.[12] Similar to most patients with anemia, serology for celiac disease and thyroid-stimulating hormone (TSH) should be considered, along with creatinine, testosterone, cortisol, and hemoglobin A1c (HbA1c) in selected cases.[13]

Treatment

Anemia of any degree should be treated when discovered and the investigations will steer the clinician toward appropriate therapy.[1] Severe (HGB <70 g/L) anemia should be treated with transfusion of packed RBCs to avoid complications. More liberal transfusion thresholds exist for patients with acute coronary syndromes (HGB 80 g/L) or early sepsis (HGB 100 g/L).[14]

Iron deficiency can be treated with dietary interventions, oral iron supplementation, and intravenous infusion. Dietary interventions should be considered for all patients but may not be sufficient in those with severe anemia or an ongoing etiology. Referral to a registered dietician should be considered. Evidence regarding the effectiveness of dietary interventions (as opposed to supplementation) is lacking. However, it is worth noting that while vegetarian diets are widely considered to predispose to iron deficiency, evidence suggests that there is no statistically significant difference in the amount of iron consumed among vegetarian or non-vegetarian diets, and that even strict vegetarians meet minimum requirements.[15]

Various dietary tips and tricks can be considered to prevent or treat anemia. In general, iron fortification in foods such as flour and noodles can be effective. Cooking in iron pots may also be effective.[16] Intestinal absorption of iron can be improved with concomitant vitamin C, either via supplementation or with drinks such as orange juice. Tea, coffee, and calcium e.g., dairy) can decrease the absorption of iron.[17]

There are various oral iron supplements available in Canada ranging in price from $5-35 per 100 mg of elemental iron. Examples of oral iron supplements available in Canada are provided in **Table 3**. Iron supplements are recommended to be taken between meals. Side effects including abdominal pain, nausea, and constipation are common.[17] QOD dosing of oral iron may decrease side effects and result in improved iron indices compared to daily dosing. This may occur from limiting the rise in hepcidin triggered by even slight rises in serum iron concentrations. Hepcidin is a circulating hormone that inhibits iron export from the liver and absorption of dietary iron through intestinal enterocytes. Dosing of oral iron on alternate days has been shown to result in lower rises in serum hepcidin compared to daily dosing.[3] It may take 3-6 months to achieve a response with oral iron so consider assessing for response at this interval.[17] Evidence is lacking to prove that newer oral iron formulations are more effective.[18] Folate deficiency can be corrected by oral or intravenous supplementation, but the underlying cause should be sought out given its rarity.

Formulation	Dose per tablet (mg)	Elemental iron per tablet (mg)	Dose
Ferrous gluconate	240	27	1-3 tablets daily or every other day*
Ferrous sulfate	325	65	1-2 tablets daily or every other day
Ferrous fumarate	325	106	1 tablet daily
Heme iron polypeptide (Proferrin)	398	11	1-3 tablets daily
Polysaccharide iron complex (Feramax)	150	150	1 tablet daily

Table 3: Oral iron formulations* available in Canada; Adapted from Ning, S et al 2019.[17]
*Take on empty stomach; avoid taking with antacid medications or proton pump inhibitors

Supplementation of other deficient micronutrients has been described elsewhere.[19]

Intravenous iron formulations are also available and are often preferable in the context of malabsorption, symptomatic anemia, intolerance to oral formulations, or when rapid replenishment is required for an intervention like surgery. IV formulations are preferred for patients with IBD for their increased efficacy as well as increased tolerability and potential for decreasing oxidative damage to the intestinal wall. It is also preferred for patients with chronic kidney disease using erythropoietin.[3] However, access to IV formulations may be limited by cost, location, and tolerability. The patient's iron deficit can be calculated using the Ganzoni formula (patient weight in kilograms x [desired HGB– current HGB g/dL] x 2.4 + 500 for adult patients). Some evidence shows that the average total iron deficit for general patients with iron deficiency anemia was about 1500 mg. Iron isomaltoside (Monoferric) allows for the fastest infusion of the most elemental iron (1000 mg or more) in a single session. Other formulations available in Canada include iron sucrose (Venofer, 300 mg) and ferrous gluconate (Ferrelict, 125 mg). These can be administered weekly until the desired amount is infused and serum HGB and iron studies can be repeated as early as 4 weeks to determine if further replenishment is necessary.[17]

Evidence of active IBD should prompt the initiation or optimization of therapy.[8] However, certain medications **(Table 2)** may need to be held or discontinued entirely if no other cause is found for the anemia.

As provided in **Table 1**, many causes of anemia are unrelated to GI pathology. Given this information, it then behooves the gastroenterologist to ensure referral or collaboration with colleagues of other disciplines. Anemia of chronic inflammation from uncontrolled extraintestinal manifestations merits collaboration with other specialties such as rheumatology and dermatology. A hematology referral could be considered if blood tests show evidence of schistocytes, pancytopenia, or macrocytic anemia without a micronutrient deficiency. A surgical referral may be required if there are surgical anastomotic issues or along with an oncology referral in the context of malignancy. The clinician should follow up after appropriate interventions to ensure resolution of the anemia and provide follow up care as necessary.

Conclusion

Management of anemia in IBD patients can be challenging because there can be multiple causes both related to and independent of the disease. Evaluation merits special attention to issues specific to and more common to patients with IBD, such as surgery, certain malignancies, and the malabsorptive and dietary issues inherent in the disease. However, iron deficiency remains the most common cause for anemia in these patients and the IBD may merit preference of IV replenishment rather than oral dosing. Irrespective of the cause, anemia should be recognized and managed without delay so as to avoid complications.

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Financial Disclosures:

Honoraria: AbbVie, Takeda, Organon, Janssen, Pfizer, and BioJamp.

References:

1. Gisbert JP, Gomollón F. Common misconceptions in the diagnosis and management of anemia in inflammatory bowel disease. Am J Gastroenterol. 2008;103(5):1299-1307. doi:10.1111/j.1572-0241.2008.01846.x
2. Patel D, Yang YX, Trivedi C, Kavani H, Xie D, Medvedeva E, et al. Incidence, duration, and management of anemia: a nationwide comparison between IBD and non-IBD populations. Inflamm Bowel Dis. 2020;26(6):934-940. doi:10.1093/ibd/izz206
3. Camaschella C. Iron deficiency. Blood. 2019;133(1):30-39. doi:10.1182/blood-2018-05-815944
4. Buttarello M. Laboratory diagnosis of anemia: are the old and new red cell parameters useful in classification and treatment, how? Int J Lab Hematol. 2016;38 Suppl 1:123-132. doi:10.1111/ijlh.12500
5. Milovanovic T, Dragasevic S, Nikolic AN, Markovic AP, Lalosevic MS, Popovic DD, et al. Anemia as a problem: GP approach. Dig Dis. 2022;40(3):370-375. doi:10.1159/000517579
6. Day AS, Yao CK, Costello SP, Andrews JM, Bryant RV. Food avoidance, restrictive eating behaviour and association with quality of life in adults with inflammatory bowel disease: a systematic scoping review. Appetite. 2021;167:105650. doi:10.1016/j.appet.2021.105650
7. Limdi JK. Dietary practices and inflammatory bowel disease. Indian J Gastroenterol. 2018;37(4):284-292. doi:10.1007/s12664-018-0890-5
8. Turner D, Ricciuto A, Lewis A, D'Amico F, Dhaliwal J, Griffiths AM, et al. STRIDE-II: an update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. Gastroenterology. 2021;160(5):1570-1583. doi:10.1053/j.gastro.2020.12.031
9. Tefferi A. Anemia in adults: a contemporary approach to diagnosis. Mayo Clin Proc. 2003;78(10):1274-1280. doi:10.4065/78.10.1274
10. Bager P, Befrits R, Wikman O, Lindgren S, Moum B, Hjortswang H, et al. The prevalence of anemia and iron deficiency in IBD outpatients in Scandinavia. Scand J Gastroenterol. 2011;46(3):304-309. doi:10.3109/00365521.2010.533382
11. Colapinto CK, O'Connor DL, Tremblay MS. Folate status of the population in the Canadian Health Measures Survey. Cmaj. 2011;183(2):E100-106. doi:10.1503/cmaj.100568
12. Gold SL, Manning L, Kohler D, Ungaro R, Sands B, Raman M. Micronutrients and their role in inflammatory bowel disease: function, assessment, supplementation, and impact on clinical outcomes including muscle health. Inflamm Bowel Dis. 2023;29(3):487-501. doi:10.1093/ibd/izac223
13. Means RTJ, Brodsky RA. Diagnostic approach to anemia in adults. In: UptoDate, Elmore JG, (Editor): Wolters Kluwer; 2024.
14. Szczepiorkowski ZM, Dunbar NM. Transfusion guidelines: when to transfuse. Hematology Am Soc Hematol Educ Program. 2013;2013:638-644. doi:10.1182/asheducation-2013.1.638
15. Rizzo NS, Jaceldo-Siegl K, Sabate J, Fraser GE. Nutrient profiles of vegetarian and nonvegetarian dietary patterns. J Acad Nutr Diet. 2013;113(12):1610-1619. doi:10.1016/j.jand.2013.06.349
16. da Silva Lopes K, Yamaji N, Rahman MO, Suto M, Takemoto Y, Garcia-Casal MN, et al. Nutrition-specific interventions for preventing and controlling anaemia throughout the life cycle: an overview of systematic reviews. Cochrane Database Syst Rev. 2021;9(9):Cd013092. doi:10.1002/14651858.CD013092.pub2
17. Ning S, Zeller MP. Management of iron deficiency. Hematology Am Soc Hematol Educ Program. 2019;2019(1):315-322. doi:10.1182/hematology.2019000034
18. Moe S, Grill AK, Allan GM. Newer iron supplements for anemia. Can Fam Physician. 2019;65(8):556.
19. Hwang C, Ross V, Mahadevan U. Micronutrient deficiencies in inflammatory bowel disease: from A to zinc. Inflamm Bowel Dis. 2012;18(10):1961-1981. doi:10.1002/ibd.22906