ANEMIA IN INFLAMMATORY BOWEL DISEASE: MORE THAN AN EXTRAINTESTINAL COMPLICATION

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ANEMIA IN INFLAMMATORY BOWEL DISEASE: MORE THAN AN EXTRAINTESTINAL COMPLICATION (Abstract). The most common hematologic complication of inflammatory bowel disease (IBD) - ulcerative colitis and Crohn’s Disease is anemia. Anemia in patients with IBD may be a result of iron, vitamin B12 or folate deficiency; anemia of chronic disease and hemolytic anemia are other causes in these patients. Factors contributing to the development of anemia include chronic gastrointestinal blood loss, vitamin B12 malabsorption secondary to terminal ileitis, folate deficiency as a result of sulfasalazine therapy. Approximately 30% of patients with IBD have hemoglobin levels below 12g/dl. The risk of developing anemia relates to disease activity, given that blood loss and inflammatory anemia are triggered by intestinal inflammation. In the management strategy of IBD patients with anemia it is important to distinguish between the different types of anemia in order to decide an appropriate manner of treatment. Keywords: INFLAMMATORY BOWEL DISEASE, ANEMIA, IRON DEFICIENCY, INFLAMMATORY ANEMIA.

Crohn’s disease and ulcerative colitis are chronic inflammatory diseases of the gastrointestinal tract, mainly affecting the small intestine and colon, which progress with relapse and remission (1). IBD is associated with extraintestinal manifestation in more than 25% of cases, including malnutrition and anemia (1, 2).

Anemia is a clinically significant state which could impair quality of life or work capability and it represents a serious comorbid condition associated with other diseases or even death (1, 3). There are two major types of anemia in IBD patients: iron deficiency anemia and inflammatory anemia called until recently anemia of chronic disease. Moreover, mixtures of the two types are commonly found in these patients (3, 4, 5).

Epidemiology of anemia in IBD. The reported prevalence of anemia in IBD is highly variable ranging from 15% up to 75% depending both on patient subgroup and definition of the disease. In hospitalized patients to prevalence is up to 70%, while in outpatients the reported prevalence is only 15% (4, 6).

Clinical manifestation. Patients may present with a diversity of symptoms and
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Sign among which the most relevant are weakness, fatigue, dyspnea, tachycardia, headaches. These signs overlap the signs of the underlying disease (7, 8, 9) (tab. I).

**Causes of anemia in IBD.** The main types of anemia in IBD patients are iron deficiency anemia and inflammatory anemia or anemia of chronic disease (3).

**TABLE I**

<table>
<thead>
<tr>
<th>Clinical consequences of anemia in IBD patients</th>
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<tbody>
<tr>
<td>Fatigue</td>
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<tr>
<td>Dyspnea</td>
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<tr>
<td>Tachycardia</td>
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<tr>
<td>Headache</td>
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<td>Dizziness</td>
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Iron deficiency anemia mainly results from chronic intestinal blood loss due to chronic inflammation of the intestinal mucosa and from reduced iron uptake from enterocytes (impaired absorption) (6, 7). Intestinal inflammation leads to a decreased serum iron level and therefore to a reduced availability of iron for erythropoiesis (6, 9). In addition, inflammatory status causes decreased iron uptake from the intestinal mucosa, hence, providing a multipart two-way pathophysiologic mechanism between iron deficiency and inflammation (3, 4).

In patients with ileal Crohn’s disease, absorption of vitamin B12 and/or folate may be impaired and all these condition frequently overlap (6, 10). Similarly, anemia in IBD patients may be induced by specific therapy-thiopurines, 5-ASA derivatives and/or by hemolysis (6, 9, 11) (tab. II).

**Anemia workup.** Full blood count, serum ferritin and C-reactive protein (CRP), are minimum requisite to identify anemia, an inflammatory relapse or iron deficiency at an early stage (7). Diagnostic measurement of blood count and CRP has been part of screening recommendations in IBD patients (11, 12). Patients in remission should be followed-up every 6 to 12 month, while active disease needs measurements at least every 3 months (11). Patients with extensive ileal Crohn’s disease, ileal resection or ileal-anal pouch need proper follow-up. Serum vitamin B12 and folic acid levels should be measured every 6 to 12 month (7, 8, 9) (tab. III).

**TABLE II**

<table>
<thead>
<tr>
<th>Etiology of anemia in IBD patients</th>
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<tbody>
<tr>
<td>Iron deficiency</td>
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<tr>
<td>Anemia of chronic disease</td>
</tr>
<tr>
<td>Vitamin B12 deficiency</td>
</tr>
<tr>
<td>Folate deficiency</td>
</tr>
<tr>
<td>Drug induced 5-ASA; Thiopurine</td>
</tr>
<tr>
<td>Hemolysis</td>
</tr>
<tr>
<td>Myelodysplastic syndrome</td>
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<tr>
<td>Aplastic anemia</td>
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</table>
The initial workup of anemia starts with the evaluation of MCV in order to distinguish between microcytosis (iron restricted anemia - iron deficiency and/or inflammatory anemia) and macrocytosis (B12 or folate deficiency) and also normocytosis (anemia of chronic disease) (8).

Platelet and white blood cell counts should be measured to reveal pancytopenia (12).

Serum ferritin level reflects the iron stores. Iron deficiency anemia is present when serum ferritin level is below 30 μg/L and hemoglobin level below 12g/L for non-pregnant females and below 13g/L for males (8).

Therefore, serum ferritin level can be used to detect iron deficiency; a drawback is that ferritin is a marker of acute inflammation and has to be evaluated together with CRP, as elevated ferritin may be due to a flair of inflammation or a superimposed infection (8, 12).

In IBD patients with anemia even transferrin concentration may not be elevated as in pure iron deficiency anemia, due to the low albumin levels found in patients with intestinal inflammation (13).

Active IBD determines elevated hepcidin levels. Hepcidin blocks intestinal iron absorption and also reduces the release of iron from stores resulting in inflammatory anemia (11, 14).

Thus, a serum ferritin level between 30 and 100 μg/L in the presence of anemia and high CRP level indicates a mixture of iron deficiency and inflammatory anemia (14). On the contrary, a serum ferritin level over 100 μg/L together with anemia and elevated CRP level indicates pure inflammatory anemia (14).

T-Sat is a measure of the iron content in the circulating transferrin. A T-Sat below 16% indicates a suboptimal source of iron for erythropoiesis (14). T-Sat level provides an indirect indication of the degree of iron use in the bone marrow but does not provide evidence of the iron stores (2). In IBD, T-Sat is used in the anemia workup in combination with ferritin and CRP, at a lower cut-off point <16% (along with ferritin level <30 μg/L suggests iron deficiency) (13).

Testing for increased sTfR distinguishes between these two types of anemia but it is not generally available yet. A high diagnostic power of sTfR or sTfR/log ferritin ratio in differentiating iron deficiency from inflammatory anemia has been suggested by several studies (13).

Drugs commonly used in IBD treatment may have myelosuppressive effects: direct (thiopurine) or indirect (antifolic effect of sulfasalazine) (11). Sulfasalazine inhibits erythropoiesis by different mechanisms: hemolysis, aplasia and/or folate absorption (12, 13). A mild anemia may be detected in patients treated with thiopurine drugs (aza-

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**TABLE III**

**Serum markers of anemia in IBD patients**

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<thead>
<tr>
<th>Mean corpuscular volume (MCV)</th>
<th>CRP</th>
<th>Serum Vitamin B\textsubscript{12}</th>
<th>Serum Folate</th>
<th>Ferritin</th>
<th>Transferrin</th>
<th>Transferrin saturation (T-Sat)</th>
<th>Hepcidin</th>
<th>Soluble transferrin receptor concentration (sTfR)</th>
</tr>
</thead>
</table>

The diagnosis of iron deficiency anemia in IBD patients may be difficult mainly when both iron and inflammatory anemia are present. In this case, laboratory measures of iron status may be unreliable, as the presence of intestinal inflammation affects the parameters of iron metabolism (12).
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Management of anemia in IBD. The correlation between disease activity and level of anemia is well known. Consequently, the most significant measure in the treatment of patients with IBD and anemia is the specific treatment of the underlying disease (12, 15).

Inflammatory anemia is a common cause of anemia among hospitalized IBD patients with active disease. Treatment of non-iron deficiency anemia may include correction of IBD specific treatment, nutritional supplements, treatment of infections and, in selected cases, erythropoiesis-stimulating agents (13, 14).

In IBD patients on biological treatment (infliximab, adalimumab) the response to therapy has been shown to determine improvement of erythropoiesis, by significantly increasing the serum transferrin level (2). Colectomy is reserved for intractable, anti-TNFα-resistant ulcerative colitis. Folic acid and vitamin B12 deficiencies, another cause of non-iron deficiency anemia, should be treated in order to avoid anemia especially in patients with Crohn’s disease, ileal resection and ileal-anal pouch (14).

Red blood cell transfusion may be considered when hemoglobin is < 7g/dL or above if risk factors and/or fatal comorbidities are present (9, 15). Nowadays transfusions in IBD patients are restricted to the severe attack of ulcerative colitis with severe anemia and hemodynamic instability, surgery for Crohn’s disease, in the presence of severe comorbidities (14, 15).

Iron replacement treatment should be started immediately after iron deficiency anemia is diagnosed. Treatment options for iron deficiency anemia are intravenous iron supplementation or oral iron administration (2, 16) (fig 1).

![Flowchart of treatment strategies for IBD patients with iron deficiency anemia.](image)

**Fig. 1.** Treatment strategies for IBD patients with iron deficiency anemia.
The therapeutic goals in iron deficiency anemia are to normalize hemoglobin, ferritin, and T-Sat levels, replenish iron stores (ferritin > 100 μg/L) and improve quality of life (17). After the initiation of martial therapy, reticulocyte count will rise in the next 7-9 days and hemoglobin in one month (18).

Oral iron therapy is indicated in patients with mild anemia, hemoglobin > 10 g/dL and remission in which oral iron absorption is not affected (17). There are many limitations of oral iron therapy: intolerance, non-compliance, worsens disease activity (14, 19).

Therefore, intravenous iron is the treatment of choice in iron deficiency anemia. According to the guidelines and consensus statement, in IBD patients intravenous iron supplementation is the preferred route. The advantage of intravenous iron therapy is better tolerance, compliance (usually single dose) and rapid reversal of anemia (18, 20, 21).

Ganzoni formula is useful to estimate iron requirements (2): Iron deficit (mg) = Body weight (kg) x [target Hb - actual (g/dL)] x 2.4 + iron stores (500mg)

CONCLUSIONS

Our analysis of the literature studies revealed that anemia is the most common extraintestinal complication of IBD. It can increase the hospitalization rate in IBD patients and can affect quality of life and work capability.

An important goal for the IBD practitioner is to use anemia markers in order to accomplish the highest diagnosis yield of anemia in IBD patients. Anemia in IBD is usually a complex manifestation of a mixed type of iron deficiency and inflammatory conditions. The gastroenterologist should keep in mind other causes of anemia especially in small intestine involvement- vitamin B12 and folate deficiency. The pathophysiological causes of anemia in IBD include malabsorption, malnutrition, inflammation, intestinal resection, drug adverse events.

Iron deficiency anemia is common in IBD patients and is difficult to diagnose in the presence of inflammation. Intravenous iron therapy is a preferable option especially in active IBD patients and moderate-severe iron deficiency anemia.

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