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Anaemia in inflammatory bowel disease – etiopathogenesis, diagnosis and treatment

Niedokrwistość w nieswoistych chorobach zapalnych jelit – etiopatogeneza, diagnostyka i leczenie

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Abstract

Anaemia is the most common extraintestinal complication of inflammatory bowel diseases in both hospitalised and outpatient patients. Symptoms associated directly with reduced haemoglobin levels as well as the consequences of iron, vitamin B_{12} or folic acid deficiency significantly impair the quality of life. Memory disorders and difficulty focusing, depression or mood swings are just some of the symptoms that can be a consequence of undiagnosed and untreated anaemia. Determination of the aetiology of anaemia in inflammatory bowel diseases, which may result not only from gastrointestinal bleeding, is important in choosing an appropriate treatment regimen. Proper diagnosis and monitoring are important in the prevention and diagnosis of anaemia. Choosing the right treatment method is the key element. Decisions regarding the use of oral or intravenous iron forms should be justified and applicable in everyday practice. The goal to be achieved is effective treatment of anaemia, which translates into improved quality of life of patients with inflammatory bowel disease. Improved comfort of life, which is so important for these patients, may be achieved regardless of the clinical activity of the underlying disease. Furthermore, proper treatment of anaemia optimises the therapy, reducing the frequency of hospitalisations and blood transfusions and, consequently, the total cost of treatment.

Keywords: inflammatory bowel disease, anaemia, iron deficiency

Streszczenie

Niedokrwistość to najczęstsze spośród pozajelitowych powikłań nieswoistych chorób zapalnych jelit zarówno u pacjentów hospitalizowanych, jak i leczonych ambulatoryjnie. Objawy związane bezpośrednio z obniżeniem stężenia hemoglobiny, jak również następstwa deficytów żelaza, witaminy B_{12} czy kwasu foliowego istotnie pogarszają jakość życia chorych. Zaburzenia pamięci i koncentracji, depresja czy zmienność nastroju to tylko niektóre symptomy, które mogą być konsekwencją nierozpoznanej i nieleczonej niedokrwistości. Określenie etiologii anemii w nieswoistych chorobach zapalnych jelit, która może być nie tylko następstwem utraty krwi do światła przewodu pokarmowego, ma znaczenie w wyborze odpowiedniego schematu leczenia. Prawidłowo prowadzone diagnostyka oraz monitorowanie są istotne w profilaktyce oraz rozpoznawaniu niedokrwistości. Kluczowym elementem jest wybór odpowiedniego sposobu leczenia. Decyzje dotyczące zastosowania doustnych bądź dożylnych preparatów żelaza powinny być odpowiednio uzasadnione i możliwe do zrealizowania w codziennej praktyce. Cel, do którego należy dążyć, to skuteczne leczenie niedokrwistości, które przekłada się na poprawę jakości życia pacjentów z nieswoistymi chorobami zapalnymi jelit. Poprawa komfortu życia, tak ważna dla chorych, osiągana jest w tym przypadku niezależnie od klinicznej aktywności choroby podstawowej. Ponadto prawidłowo prowadzone leczenie niedokrwistości powoduje optymalizację terapii, zmniejszenie częstości hospitalizacji oraz spadek częstości przetaczania krwi, a co za tym idzie – obniżenie całkowitych kosztów leczenia.

Słowa kluczowe: nieswoiste choroby zapalne jelit, niedokrwistość, niedobór żelaza

INTRODUCTION

Inflammatory bowel diseases (IBD), which include ulcerative colitis (UC) and Crohn's disease (CD), are chronic gastrointestinal disorders with complex, multifactorial and not fully understood aetiology, which are characterised by exacerbations and remissions. Significant importance is attributed to interactions between immune disorders, genetic and environmental factors. Abdominal pain, diarrhoea and bloody stools are the most common symptoms reported by patients with IBD. Extraintestinal manifestations may involve almost every organ or system; however, the most commonly involved include joints (e.g. peripheral arthritis or sacroiliac arthritis), skin (erythema nodosum or pyoderma gangrenosum), eyes (e.g. uveitis or iritis) and bile ducts (e.g. primary sclerosing cholangitis)[1,2]. They may develop as the first symptoms of IBD, accompany exacerbations or occur independently of IBD activity. It is assumed that extraintestinal manifestations affect up to 36% of IBD patients[1]. Anaemia, which may occur in up to 74% of patients, depending on the definition used and the population assessed, is the most common extraintestinal manifestation[3,4]. Anaemia is more often diagnosed in hospitalised vs. outpatient patients (~68% and ~16%, respectively). Importantly, this problem occurs in about 42% of patients within the first year of IBD diagnosis, with recurrences within 10 months of therapy completion in 50% of patients[5].

Due to such a high incidence of anaemia in patients with UC and CD, anaemia in IBD is regarded as an inevitable symptom of the disease and, consequently, underdiagnosed and inappropriately managed[6,7]. Anaemia is known to significantly impair the functioning of IBD patients, affecting their quality of life and ability to work, regardless of the activity of the underlying disease[8,9]. Anaemia is also a common cause of hospital stays and blood transfusions in patients with IBD. The lack of diagnosis and effective treatment of anaemia in IBD results in the need for intravenous iron supplementation and/or blood transfusion, which are, in turn, associated with adverse effects, the risk of alloimmunisation and viral infections[10].

AETIOPATHOGENESIS OF ANAEMIA IN IBD

Although IBD-related anaemia is multifactorial, its diagnosed forms are usually caused by impaired iron metabolism (Tab. 1)[11]. Similarly to the general population, iron deficiency anaemia (IDA) dominates in IBD patients, followed by anaemia of chronic disease (ACD)[12]. Iron deficiency is observed in patients with IBD long before haemoglobin decline and is primarily the result of poor dietary intake of iron, impaired absorption and slow blood loss through the damaged intestinal mucosa[13]. Increasingly more attention is paid by researchers to non-anaemic iron deficiency in IBD patients[12,14]. It is believed that iron deficiency in IBD is more common than IDA, which should be regarded as a final, evident manifestation of iron deficiency[15]. According to current reports, iron deficiency may occur in 36–90% (mean 45%) of patients with IBD[7,12,16].

Common	• Iron deficiency anaemia • Anaemia of chronic disease
Rare	• Vitamin B_{12} deficiency • Folic acid deficiency • Drug-induced anaemia (sulfasalazine, thiopurines, methotrexate)
Very rare	• Congenital haemoglobinopathies and impaired erythropoiesis • Aplastic anaemia • Myelodysplastic syndrome • Haemolysis

Tab. 1. Causes of anaemia in IBD[11]

Acute or chronic inflammation is a very important factor affecting iron homeostasis in patients with IBD. Inflammation, which may occur not only during disease exacerbations in this patient population, disturbs iron metabolism, leading to the so-called functional iron deficiency and ACD[17]. Increased production of proinflammatory cytokines stimulates the synthesis of hepcidin in the liver. Hepcidin is a direct inhibitor of a protein responsible for exporting iron from a cell, i.e. ferroportin[18]. The mechanism of action of hepcidin is associated with inhibiting duodenal iron absorption and blocking access to reticuloendothelial system macrophage iron pools. Hepcidin reduces plasma iron pools, and thus iron availability for erythropoiesis, leading to anaemia of chronic disease[17,19]. This mechanism may co-occur with the above mentioned causes of iron deficiency in patients with IBD (gastrointestinal bleeding, poor dietary intake of iron, malabsorption through inflamed mucosa)[20]. Therefore, ACD coexisting with IDA, which results in the so-called combined anaemia, for which ion supplementation should be considered, is more common in patients with CD and UC compared to the general population[13].

Anaemia in patients with IBD may be also caused by adverse effects of drugs. Thiopurines and methotrexate may contribute to bone marrow damage. Sulfasalazine may cause blood cell haemolysis and bone marrow aplasia[21]. Furthermore, sulfasalazine and methotrexate reduce the absorption of folic acid, thus contributing to its deficiency.

Isolated megaloblastic anaemia is rare in patients with IBD. Since no macrocytosis is usually observed due to the accompanying iron deficiency, monitoring of cobalamin and folic acid levels is important. Vitamin B_{12} or folic acid deficiency in patients with IBD is particularly common after resection of the ileum[22]. These two vitamins are absorbed in the final segment of the ileum. Therefore, patients after ileal-ileocecal resection, with inflamed or fibrotic final section of the small intestine and an interloop fistula excluding this final section of the small intestine

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Group	Haemoglobin [g/dL]	Haematocrit [%]
Children aged between 6 months to 5 years	11	33
Children aged 5–11 years	11.5	34
Children aged >12 years	12	36
Non-pregnant adult women	12	36
Pregnant women	11	33
Adult men	13	39

Tab. 2. Lower limit of normal for haemoglobin and haematocrit according to the World Health Organization[26]

from passage, are at an increased risk of cobalamin and folic acid deficiency[23]. Furthermore, in addition to the above mentioned causes, folic acid deficiency may be caused by IBD therapy (methotrexate, sulfasalazine), parenteral nutrition and diet poor in fresh vegetables. Recent studies showed vitamin B_{12} deficiency in 15–22% of patients with CD and 2.8–7.5% of patients with UC. Folic acid deficiency was reported in 22–28.8% and 4.3–8.6% of patients, respectively[22,24].

Other causes of anaemia in IBD are much less common and occur at rates comparable to those in the general population.

Considering the variable aetiology of IBD, proper diagnosis seems crucial for effective treatment.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF ANAEMIA IN IBD

Anaemia is a pathological condition in which the amount of red blood cells and haemoglobin is insufficient for normal oxygen supply to tissues and organs[25]. Anaemia is defined as haemoglobin, haematocrit and red blood cells of at least 2 standard deviations below standard values. Tab. 2 shows minimum normal age- and sex-based haemoglobin and haematocrit values, as in accordance with the World Health Organization criteria[26]. Although these criteria have been developed for the general population, they are also used in patients with IBD and should be targeted in the treatment of anaemia in this group of patients[6].

Since the aetiology of anaemia in IBD is variable and its causes may overlap during different phases of the disease, proper diagnosis is necessary to determine aetiological factors and pathomechanisms underlying decreased haemoglobin, which allows for the choice of effective therapy. From a practical point of view, anaemia classification based on the mean corpuscular volume (MCV) is most useful in the differential diagnosis of anaemia. In simple terms, iron deficiency anaemia occurs in microcytosis, anaemia of chronic disease occurs in normocytosis, whereas anaemia induced by vitamin B_{12} or folic acid deficiency is observed in macrocytosis. Reticulocyte count, which informs about bone marrow's ability to respond to the developing anaemia and the effectiveness of treatment used, provides important data. Increased reticulocyte count indicates normal erythrocyte formation, whereas low or normal reticulocyte count may be associated with impaired erythropoiesis or bone marrow disease. In the case of suspected haemolytic aetiology of anaemia, serum lactate dehydrogenase activity (decline), haptoglobin levels (decline) and unconjugated bilirubin (increase) should be measured. Leukopenia, pancytopenia or abnormal blood smear, such as neutropenia, immature precursors or hairy cells direct the diagnosis to haematological conditions.

In relation to the epidemiology of anaemia in IBD, in addition to peripheral blood cell count, an assessment of iron metabolism indicators is the primary management. Serum iron measurement alone is insufficient for the assessment of iron metabolism. Iron levels show high intra-individual biological variability and a circadian rhythm (evening levels are 20% lower compared to morning levels). Reduced iron levels are observed in both iron deficit (iron deficiency, iron deficiency anaemia) as well as in impaired availability of iron in response to inflammation (functional iron deficiency, iron deficiency in chronic disease). Therefore, it is necessary to use specific parameters allowing for determining the amount of both circulating and stored iron for the assessment of iron metabolism to be reliable. To this end, ferritin and transferrin saturation should be measured. Since ferritin is an acute phase protein, its levels should be interpreted according to disease activity (e.g. by measuring C-reactive protein, CRP). Ferritin levels <30 μg/L and transferrin saturation <16% in patients with no biochemical inflammatory markers are indicative of iron deficiency. In the case of active inflammation, ferritin levels ranging between 100 and 800 μg/L indicate normal iron pool. Diagnostic criteria for ACD include ferritin levels >100 μg/L and transferrin saturation <16% in the presence of clinical or biochemical inflammatory markers. For persistent ferritin levels of 30–100 μg/L, a combination of IDA and ACD is most likely. Criteria presented in Tab. 3 may be useful for the differential diagnosis of these two types of anaemia.

Soluble transferrin receptor (sTfR) is a reliable parameter in the differential diagnosis of iron deficiency coexisting with inflammation. Increased sTfR in patients with active inflammation and normal ferritin levels indicates poor iron pool in the body, and thus combined iron deficiency[27]. However, the use of sTfR measurement is limited in daily practice due to the poor availability of the sTfR assay in medical laboratories.

According to the guidelines of the European Crohn's and Colitis Organisation (ECCO) and the Working Group of the Polish National Consultant in Gastroenterology, patients with IBD should have their haemoglobin, ferritin and CRP checked every 6–12 months during remission and every 3 months during increased inflammatory activity[28,29]. It is also recommended to evaluate transferrin saturation, which requires the measurement of total iron

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binding capacity (TIBC). Patients at a high risk of vitamin B_{12} or folic acid deficiency (with a history of small intestine resections or with small bowel lesions and a pouch) and those with macrocytosis should have their vitamin B_{12} or folic acid measured at least once a year.

TREATMENT

The treatment of anaemia in patients with IBD is targeted not only at haemoglobin normalisation, but most of all at life quality improvement, reduced number and duration of hospital stays and prevention of blood transfusions. Authors of the publication from 2017 drew attention to the fact that compensation of iron deficiency in IBD improves the quality of life in both patients with anaemia and those with iron deficiency[30]. Iron is a component of not only haemoglobin and myoglobin, but it is also found in cytochromes and multiple enzymes; therefore, its deficiency may manifest independently of anaemia. Iron deficiency significantly affects cognitive functions by compromising learning and memory; it may also cause sleep disorders, loss of libido, and restless legs syndrome[31]. Other symptoms of iron deficiency include dry skin, angular cheilitis, brittle and fragile nails with ridges, brittle and thinning hair.

The clinical picture of anaemia depends on the rate and the degree of its progression as well as on multiple individual factors, such as age, sex, general condition and comorbidities. In the case of slow progression of anaemia, the body develops adaptation mechanisms allowing for tissue adaptation to reduced oxygen supply, which is not seen in rapidly increasing blood loss. Cardiovascular and respiratory efficiency plays an important role in the manifestation of anaemia. A young person with no significant comorbidities may experience the symptoms of anaemia only when haemoglobin levels fall to about 7–8 g/dL. Older patients, particularly those with coexisting cardiovascular and respiratory failure, may gradually develop symptoms of anaemia at a haemoglobin decline to 10–12 g/dL, which are initially experienced during exercise and then also at rest. Typical symptoms of anaemia other than pale skin and mucosa include fatigue and fatigability, tachycardia, dyspnoea, headaches and dizziness.

Laboratory parameter	Anaemia		
	Iron deficiency	Chronic disease	Combined
Haemoglobin	↓	↓	↓
MCV	↓	Normal or ↓	Normal or ↓
Serum ferritin	↓	↑	Normal or ↑
Transferrin saturation	↓	↓	↓
Soluble transferrin receptor	↑	Normal	Normal or ↑
Serum iron	↓	↓	↓
CRP	Normal	↑	↑

MCV – mean corpuscular volume.

Tab. 3. Differential diagnosis of iron deficiency anaemia (IDA) and anaemia of chronic disease (ACD)

A decision on treatment initiation and the therapeutic method depends on many factors, with the most important being the patient's general condition, IBD activity, the severity of anaemia, and the risk of potential adverse effects. According to the ECCO guidelines, the use of oral iron should be considered for patients in remission, with mild anaemia, and with no history of adverse effects (abdominal pain, nausea, diarrhoea, constipations) after this form of therapy. Oral iron supplementation is the most convenient form of treatment of iron deficiency anaemia, and should be continued for 4–6 months after blood cell count normalisation. Oral iron is available in the form of Fe^{2+} salts (sulphate, gluconate, succinate) and Fe^{3+} hydroxides. Since iron hydroxide does not interact with drugs and does not form insoluble compounds with food components, it may be taken regardless of meals. Divalent iron, which is most often contained in preparations, undergoes oxidation in the intestine, giving rise to free hydroxyl radicals (Fenton's reaction), which are toxic for the mucosa. The resulting symptoms of intolerance, such as nausea, diarrhoea, constipations, flatulence and abdominal pain, may lead to treatment discontinuation in about 20% of patients with IBD[32,33]. This is particularly important in this group of patients, in whom long-acting iron preparations should be avoided as they release iron also in the distal part of intestines, where it is not absorbed[33]. Oral iron preparations may also affect intestinal microbiota and increase the levels of calprotectin, a marker of intestinal inflammation[34]. Therefore, 100 mg of elemental iron is considered to be an effective daily dose for patients with IBD.

Intravenous supplementation is recommended for patients intolerant to oral therapies. According to the ECCO guidelines and the recommendations of the Working Group of the Polish National Consultant in Gastroenterology, intravenous iron supplementation for the treatment of anaemia should be used in patients with severe IBD attack, anaemia with haemoglobin below 10 g/dL, with a history of ineffective or not tolerated oral iron therapy, and during erythropoietin treatment[28,29].

It was pointed out in a 2015 meta-analysis (13 articles, 2,906 patients with anaemia in IBD) that intravenous iron supplementation more effectively increased haemoglobin and ferritin levels in moderate-to-severe anaemia[35]. Iron deficiency should be estimated before initiating intravenous iron supplementation. Until recently, the Ganzoni equation was a commonly used method:

iron deficiency (mg) = body weight (kg) × [target haemoglobin – actual haemoglobin (g/dL)] × 2.4 + iron stores (500 mg or 15 mg/kg in patients with body weight <35 kg)

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Haemoglobin [g/dL]	Body weight <70 kg	Body weight >70 kg
>10	1,000 mg	1,500 mg
<10	1,500 mg	2,000 mg

Tab. 4. Simplified estimation of total iron needed[36]

However, latest research indicates that the calculated iron deficiency does not correspond to the actual one. Such conclusions were drawn, among others, by the authors of a clinical trial using ferric carboxymaltose, in which full dose (calculated based on the Ganzoni equation) allowed reaching ferritin levels of 100–800 μg/L in only 26.5% of patients. A simpler and more effective method for the measurement of iron deficiency was used in the FERGIcor trial and compared with the Ganzoni method[36]. This alternative iron dosage regimen is based on baseline haemoglobin and body weight (Tab. 4). When using this method, it should be kept in mind that an additional iron dose of 500 mg should be administered in patients with haemoglobin below 7 g/dL.

Depending on the carrier (Fe^{3+} ion in all cases), intravenous formulations differ in their pharmacological and biological properties, which translates in the clinical practice into the maximum size of a single and a total dose, acceptable duration of a single transfusion as well as the need for a test dose and the risk of severe adverse effects. Intravenous preparations currently available on the Polish market include iron sucrose (Venofer), iron dextran (Cosmofer), iron isomaltoside (Monover) and ferric carboxymaltose (Ferinject). The use of intravenous iron formulations is also associated with the risk of adverse effects, the most severe of which are anaphylactic shock, hypotension, tachycardia and bronchospasm. Their incidence depends on the iron complex used[37]. Currently, a test dose is required only for iron-hydroxide dextran complex. A 30-minute observation period is recommended following infusion of each preparation. There are well-known risk factors for hypersensitivity reaction, including previous hypersensitivity reaction after iron infusion, very rapid iron infusion, drug allergy, severe atopic dermatitis, and systemic inflammatory disease[37]. Recently, an interesting paper on this subject has been published. It was a retrospective analysis of more than 6,000 patients with IBD who received a total of 37,168 IV iron infusions (3 times on average). All commercially available forms of intravenous iron were used for supplementation. The incidence of adverse effects was low. Only 1.3% of IBD patients experienced adverse effects. Hypertension accounted for the majority of cases (76). The risk of the most serious adverse effect, i.e. anaphylactic shock, was estimated at 0.24 events per 1,000 iron infusions. Hypophosphatemia, which was not considered in the above mentioned study, is an adverse effect of IV iron supplementation. The risk of hypophosphatemia increases in the case of frequent iron infusions, low baseline ferritin and coexisting malnutrition[38].

The choice of iron formulation and the route of administration should be individual for each patient and compliant with the current guidelines. Normalised or increased haemoglobin (by at least 2 g/dL after 4 weeks) indicates good response to iron therapy used (either oral or intravenous). In the case of lack of response to an intravenous iron therapy (after 4 weeks of treatment), erythropoiesis-stimulating agents (epoetin α and β, darbepoetin α) should be considered. Such management allows for the use of intravenous iron in the mechanism of erythropoietin stimulation of red blood cell precursors and prevents iron entrapment in the reticuloendothelial system. The use of erythropoiesis-stimulating agents is justified in anaemia in chronic disease, especially at haemoglobin levels below 10 g/dL. However, it should be noted that the treatment of the underlying disease, which is intended to control inflammation and normalise the mechanisms responsible for iron metabolism, is of key importance.

Patients with symptomatic or severe anaemia (haemoglobin below 7 g/dL) require blood transfusion in the first place. In severe IBD attack, blood transfusion should be continued until haemoglobin levels above 10 g/dL are reached[39]. It should be kept in mind, however, that repeated blood transfusion increases the risk of antibody production; therefore, it should be limited to exceptional, urgent cases. After transfusion, patient's condition should be monitored and IV iron supplementation should be planned, even if haemoglobin levels are normal.

Once anaemia treatment is completed, follow-up measurements of haemoglobin, ferritin, CRP and transferrin saturation at 3-month intervals for at least a year are recommended in patients with IBD. Such management is intended to prevent recurrent iron deficiency, which was observed in 50% of patients with IBD after 10 months of treatment completion[36]. The higher the ferritin levels reached after treatment completion (the lowest risk >400 μg/L), the lower the risk[40]. According to the ECCO guidelines, another IV iron supplementation should be considered when ferritin levels drop below 100 μg/L or haemoglobin levels are below 12 g/dL in women and 13 g/dL in men. On the other hand, excessive total iron dose increases the risk of iatrogenic hemosiderosis, which is unlikely to occur in patients with IBD and a tendency to chronic bleeding. Ferritin levels above 800 μg/L and transferrin saturation of more than 50% indicate iron overload.

If vitamin B_{12} or folic acid deficiency is diagnosed, it should be supplemented. Vitamin B_{12} deficiency may lead to cognitive impairment, depression, mania, mood swings and delusions. The clinical picture of cobalamin deficiency is dominated by neurological symptoms, the severity of which is not directly correlated with the severity of anaemia. Hand and foot paresthesia, limb numbness, gait instability due to impaired deep sensation, poor vision or abnormal tendon and extrapyramidal reflexes are common manifestations of vitamin B_{12} deficiency. Furthermore, physical examination may reveal premature greying of hair, and a smoothened, dark-red tongue. Patients also report burning tongue and loss of taste. Clinical manifestations of folic acid deficiency,

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which are not directly related to anaemia, are the same as those described above for vitamin B_{12} deficiency except for neurological symptoms.

The treatment of vitamin B_{12} deficiency involves intramuscular administration of cyanocobalamin at a dose of 1,000 μg once daily for 7–14 days, and then once a week for 4–8 weeks. Maintenance treatment (1,000 μg once a month) is recommended in cases of permanent malabsorption. In the case of folic acid deficiency anaemia, oral supplementation is used for 1–4 months or until haematological parameters normalisation is achieved. Folic acid dose depends on the aetiology of anaemia and usually ranges between 5 and 20 mg/day.

CONCLUSIONS

There seems to be a clear need to treat anaemia in inflammatory bowel disease. It should be noted that the aetiology of anaemia in IBD is varied and that the causes of anaemia may be coexisting, depending on the phase of the disease. However, these are usually iron deficiency anaemia and anaemia of chronic disease. It is also important to exclude vitamin B_{12} and folic acid deficiency. Proper diagnosis to determine the type of anaemia and the underlying pathologies is of key importance for the choice of treatment strategy and therapeutic decisions on the mode of treatment in patients with IBD.

Effective treatment of anaemia improves the quality of life in patients with IBD, which is achievable regardless of the clinical activity of the disease. Conscious monitoring of patients with IBD for anaemia, iron deficiency, along with proper treatment of anaemia allow for both optimised therapy and reduced total treatment costs.

Conflict of interest

The authors do not report any financial or personal connections with other persons or organisations that could adversely affect the content of the publication and claim the right to publish it.

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