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Guidelines

Diagnosis and management of anemia in pediatric inflammatory bowel diseases: Clinical practice guidelines on behalf of the SIGENP IBD Working group

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ABSTRACT

Anemia is one of the most frequent extra-intestinal manifestations of inflammatory bowel disease. Insidious onset, variability of symptoms and lack of standardized screening practices may increase the risk of underestimating its burden in children with IBD. Despite its relevance and peculiarity in everyday clinical practice, this topic is only dealt with in a few documents specifically for the pediatric field. The aim of the current guidelines is therefore to provide pediatric gastroenterologists with a practical update to support the clinical and therapeutic management of children with IBD and anemia.

A panel of 19 pediatric gastroenterologists and 1 pediatric hematologist with experience in the field of pediatric IBD was agreed by IBD Working group of the Italian Society of Gastroenterology, Hepatology and Nutrition (SIGENP) to produce the present article outlining practical clinical approaches to the pediatric patient with IBD and anemia. The levels of evidence and recommendations have been defined for each part of the statement according to the GRADE system.

Introduction

Anemia is one of the most frequent extra-intestinal manifestations of inflammatory bowel disease (IBD) [1–4]. The etiology of anemia in IBD is complex and multifactorial, including iron deficiency (ID), anemia of chronic disease (ACD), vitamin deficiencies, hemolysis, or exposure to myelosuppressive medications. The prevalence of anemia in children with IBD has not yet been precisely established, although it may even be higher than that in adults, considering the more frequent presence of extensive involvement, severe phenotypes and poor nutritional status, particularly at diagnosis [5,6]. In addition, the insidious onset, variability in symptoms, and lack of standardized screening practices may in-

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crease the risk of underestimating burden in children with IBD. In fact, pediatric gastroenterologists seem to give treatment a low priority, regardless of its impact on clinical management and the patient's health-related quality of life [7–9]. On the other hand, the advent of the new therapeutic strategies, which have certainly improved the management of IBD-related anemia management, are not yet approved for young children and infants. Only a few documents have specifically addressed this topic for the pediatric setting, despite its relevance and peculiarity in daily clinical practice [10,11]. Therefore, the aim of the current guidelines is to provide a practical update for pediatric gastroenterologists to support the clinical and therapeutic management of children with IBD and anemia.

Methods

A panel of 19 pediatric gastroenterologists with experience in the field of pediatric IBD and 1 pediatric hematologist was selected in April 2021 following an open call among the members of the Italian Society of Gastroenterology, Hepatology and Nutrition (SIGENP) IBD Working group. The first web-meeting led to the organization of the position paper into 5 subparagraphs: 1) *Definition, incidence, and pathophysiology;* 2) *Clinical presentation, assessment and diagnosis*; 3) *Iron deficiency anemia*; 4) *Other types of anemia*; 5) *Refractory anemia*. One of five different sub-working groups were assigned to each paragraph. The key questions were developed following the PICO format and voted on. Each working group was asked to perform a literature search within their specific topic using Medline-PubMed database with appropriate search strategies using a last search date of May 31st, 2022 (Supplementary Table 1). The levels of evidence and recommendations have been defined for each part of the statement according to the GRADE system. Statements of specific recommendation were produced by each subgroup and discussed in a second web-meeting in July 2022. The document was revised after receiving the comments from the reviewers following the first submission. A second round of electronic voting was performed on December 2023. Finally, 17 recommendations and 10 statements were voted and accepted if at least 80% agreement was reached. The guideline includes recommendations, statements and practice points, reflecting common practice where evidence is lacking.

1. Definition, incidence and pathophysiology

Q1. What is the most appropriate definition of anemia in children with IBD?

Recommendation:

1.1. The definition of anemia in children with IBD should rely on currently validated WHO criteria

[strong recommendation, low quality of evidence] [Vote result: Agree: 90 %, neutral: 0 %, disagree: 10 %]

Statement:

1.2. The main types of anemia in IBD children are iron deficiency anemia, anemia of chronic disease and anemia of mixed origin

[low quality of evidence] [Vote result: Agree: 100 %, neutral: 0 %, disagree: 0 %]

Practice points:

- Iron deficiency anemia should be diagnosed in presence of ferritin<30 µg/L or < 100 µg/L in the absence/presence of active disease, respectively.
- In the presence of inflammation, anemia of chronic disease is diagnosed when serum ferritin>100 µg/L and transferrin saturation<20%.

Summary of evidence

According to the World Health Organization (WHO), anemia is defined as low hemoglobin (Hb) or red cell mass which can result in a reduced ability of the blood to carry oxygen to the body's tissues [12,13]. Although the normal range of Hb varies with age, gender and race, the indicated thresholds should be considered for the diagnosis (Table 1). The anemia in IBD has a complex and multifactorial etiology and represents a prototype of the combination of iron deficiency anemia (IDA), secondary to chronic blood loss, and ACD, with impaired iron absorption due to tissue inflammation [1,14-19]. IDA and ACD often overlap and knowing the etiology of anemia is critical for proper management. IDA diagnostic criteria may differ depending on whether the patient is in remission or in the active phase of the disease [20]. Therefore, IDA should be diagnosed in the presence of ferritin <30 µg/L or < 100 µg/L in the absence/presence of active disease, respectively [21,22]. Inflammation, on the other hand, through mechanisms mediated by cytokines, increases levels of circulating hepcidin, which binds to and disables the iron transporter, ferroportin. Under the influence of hepcidin, export of intracellular iron is stalled, trapped within the enterocytes and macrophages. Thereby, insufficient utilizable iron is available for erythropoiesis despite adequate iron stores, inducing a so called "functional" iron deficiency [23–25]. Thus, in the presence of biochemical or/and clinical evidence of inflammation, ACD should be diagnosed if serum ferritin>100 µg/L and transferrin saturation< 20% [10]. Other causes are less common but should be taking into account, including vitamin deficiencies (such as vitamin B12 and folate), hemolysis, or some cases related to bone marrow suppressant drugs [14,22,25-27] (Table 2).

Q2. What is the current incidence of anemia in children with IBD?

Statements:

1.3. Anemia is the most frequent extra-intestinal manifestation of pediatric IBD, although its incidence has not been fully established

[low quality of evidence] [Vote result: Agree: 100 %, neutral: 0 %, disagree: 0 %]

1.4. Children with IBD have a higher risk of anemia than the general population and adult patients with IBD

[low quality of evidence] [Vote result: Agree: 90 %, neutral: 10 %, disagree: 0 %]

Table 1
WHO classification of anemia according to age and severity.

	ANEMIA (Hb, g/dL)		
Population	Mild	Moderate	Severe
6 months-5 years	10–10.9	7–9.9	<8
6–11 years	11–11.4	8–10.9	<8
12–14 years	11–11.9	8–10.9	<8
Non pregnant female ≥ 15 years			
Pregnant female ≥ 15 years	10–10.9	7–9.9	<7
Male ≥ 15 years	11–12.9	8–10.9	<8

Abbreviations: Hb: Haemoglobin.
Adapted from [8]: World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Published 2011. Accessed June 29, 2021. https://apps.who.int/iris/bitstream/handle/10,665/85,839/WHO_NMH_NHD_MNM_11.1_eng.pdf?ua=1.

Table 2
Other causes of non iron deficiency anemia in pediatric IBD.

Common	Anaemia of chronic disease
Occasional	Vitamin deficiency: - Cobalamin - folate Drug related: - Sulphasalazine - 5-aminosalicylic acid - Azathioprine - 6-mercaptopurine
Rare	Autoimmune hemolysis Chronic Renal Insufficiency Anemia in liver disease Myelodysplastic syndrome Red blood cell aplasia Glucose-6-phosphate dehydrogenase deficiency Congenital hemoglobinopathies

1.5. ***Iron deficiency anemia is the most common form of anemia that occurs in IBD***

[low quality of evidence] [Vote result: Agree: 90 %, neutral: 0 %, disagree: 10 %]

Summary of evidence

The prevalence of anemia in patients with IBD ranges from 8% to 73% depending on the patient subpopulation, while in the general population, the overall prevalence of anemia is 47% in preschool-age children and 25% in school-age children [28,29]. Approximately, two-thirds of adults with IBD have anemia at diagnosis and the prevalence and causes of anemia may change during follow-up [30,31]. The true prevalence of IDA in the pediatric population with IBD remains unknown, with studies reporting higher rates than in the adult population. In 2012, an observational study reported a higher prevalence of IDA in IBD children (70%) and adolescents (42%) than in adults (40%) [32]. In 2016 Martinelli and colleagues identified a prevalence of anemia of 34% in a cohort of 50 children with IBD [23]. Among the anemic children 17.6% had IDA, 11.7% ACD and 70.5% a combination of IDA and ACD [23]. Recently, a retrospective study of pediatric patients with IBD reported a prevalence of 28% of IDA or a combination of IDA and ACD at diagnosis and 15% at the 1-year follow-up [33].

Q3. Are there certain risk factors associated with developing anemia in children with IBD?

Statements:

1.6. Pediatric age is an independent risk factor for anemia in IBD

[low quality of evidence] [Vote result: Agree: 85 %, neutral: 5 %, disagree: 10 %]

1.7. Active and severe disease is the strongest predictor for the development of anemia in IBD

[low quality of evidence] [Vote result: Agree: 100 %, neutral: 0 %, disagree: 0 %]

Practice point:

Nutritional status, as reflected in body mass index and albumin levels, can influence the development of anemia in IBD

Summary of evidence

Pediatric age is an independent risk factor for anemia in IBD. Sjoberg et al. reported a higher prevalence of anemia in children than adults, both at diagnosis and after 1 year of follow-up [34]. Similarly, Goodhand et al. found that anemia was more common in children compared to young adult and adult IBD patients [32]. Several risk factors have been associated with the development of anemia in IBD. Considering the type, extent and severity of the IBD disease, Shentova-Eneva et al. found that the prevalence of anemia was 60% in the Ulcerative Colitis (UC) patients and 77% in the Crohn's disease (CD) patients. Of UC patients with anemia, 37% had pancolitis, 18% extensive disease, 33% left-sided colitis and 11% ulcerative proctitis. Of CD patients with anemia, 81% had ileocolonic disease, 11% colonic disease and 7% ileal disease [35]. Active and severe disease, as reflected by elevated C reactive protein (CRP) or erythrocyte sedimentation rate (ESR), is the strongest predictor of anemia in children with IBD [35–39]. Interestingly, measures of clinical indices of disease severity, namely pediatric Crohn's disease Activity index (PCDAI) and pediatric Ulcerative Colitis activity index (PUCAI), poorly correlate with the degree of anemia, particularly in mild disease [35]. Nutritional status influences the development of anemia in pediatric IBD. A study by Gerasimidis K et al. found a lower body mass index and a lower albumin level in anemic children with CD than in non-anemics [40]. After an 8-weeks course of exclusive enteral nutrition, severe anemia decreased (32% versus 9%; $p = 0.001$) and the Hb concentration increased by 0.75 g/dL. Furthermore, analyses comparing the proportions of African-Americans and non-African-Americans in children with IBD showed that African-Americans had lower Hb at diagnosis than non-African Americans [41].

2. Clinical presentation, assessment and diagnosis

Q4. What are the clinical signs of anemia in children with IBD?

Statement:

2.1. Anemia can cause a variety of symptoms depending on the type, severity, and onset

[low quality of evidence] [Vote result: Agree: 100 %, neutral: 0 %, disagree: 0 %]

Anemia can cause a variety of symptoms depending on the severity, rate and timing of the decrease in Hb, chronicity and comorbid conditions [11,42]. An acute decrease in Hb levels can impact the circulatory and cardiovascular systems and results in symptoms mainly related to hypoxia (increased heart rate, systolic murmur, syncope or even cardiovascular insufficiency). Symptoms of chronic anemia include dizziness, shortness of breath, fatigue, nausea, irritability, delayed growth and development [43]. Neurological symptoms such as poor concentration, attention deficit disorder, hyperactivity disorder, restless legs syndrome and eating disorders such as pica and pagophagia (ice craving) have also been observed [44–48]. Prolonged deficiency can also lead to epithelial changes leading to dry mouth, cheilitis, atrophic glossitis, hair loss and, rarely, Plummer-Vinson syndrome [49].

Q5. When should we assess anemia in children with IBD?

Recommendation:

2.2. Screening for anemia should be routinely performed in all children with IBD

[strong recommendation, low quality of evidence] [Vote result: Agree: 100 %, neutral: 0 %, disagree: 0 %]

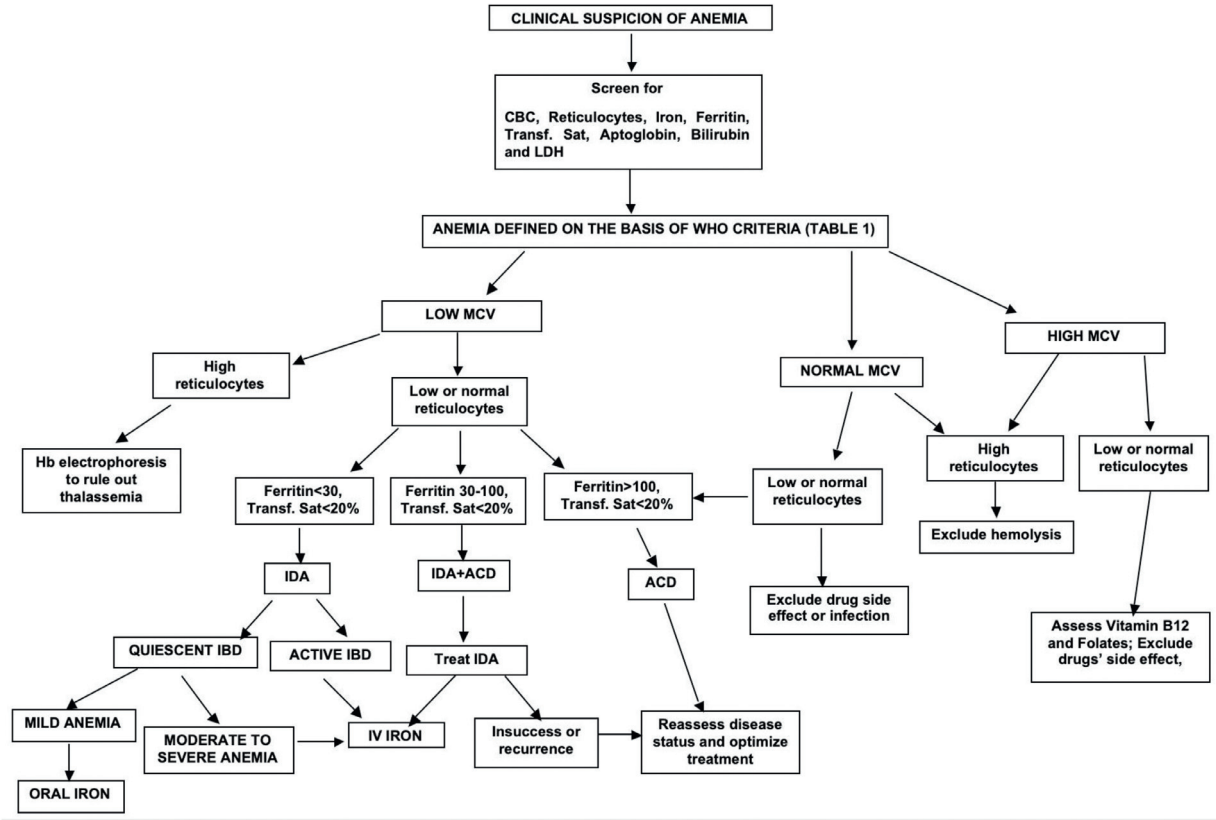

Fig. 1. Practical algorithm for the management of diagnosis and treatment of anemia in children with IBD.
Abbreviations: CBC: complete blood count; LDH: lactic dehydrogenase; ACD: anemia of chronic disease; IDA: iron deficiency anemia; MCV: mean corpuscular volume; IBD: inflammatory bowel disease; IV: intravenous.

Practice point:

Screening for anemia should be performed at diagnosis, every 3 months in active disease and every 6–12 months in patients in remission or mild disease.

Q6. What tests are indicated for anemia work-up?

Recommendation:

2.3. Screening for anemia should include evaluation of hematological parameters, micronutrients deficiencies, drug toxicity, hemolysis, and inflammatory indexes

[strong recommendation, low quality of evidence] [Vote result: Agree: 85 %, neutral: 5 %, disagree: 10 %]

Practice points:

- Minimal work-up for inactive disease should include complete blood count (CBC), CRP, ferritin levels. If active disease occurs, patients should have a CBC, including mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), red cell distribution width (RDW), and reticulocytes, serum iron and ferritin, transferrin saturation, haptoglobin, bilirubin and lactic dehydrogenase.
- Work-up of patients with active ileal disease, prior surgery or on chronic therapy with sulfasalazine, thiopurines or methotrexate (MTX), should include a CBC, including MCV, vitamin B12 and folic acid and should be performed at least annually.
- In the diagnostic work-up of vitamin B12 and folate deficiency, methylmalonic acid (MMA) and homocysteine levels should be included.

Summary of evidence

Screening for anemia should be included in the biochemical assessment plan at diagnosis and repeated based on disease activity [1,6]. In case of active disease, laboratory assessment of anemia should be performed every 3 months, while in patients in remission or mild disease every 6–12 months [1,50]. The recommended schedules reflect standard clinical practice but do not apply to hospitalized patients [1]. According to the European Crohn's and Colitis Organization (ECCO) guidelines for adults with IBD, a CBC, CRP, and serum ferritin are minimum requirements to detect anemia, an inflammatory flare, or ID at an early stage [1]. From the assessment of CBC, including MCV and MCH, anemia is more likely to be microcytic and hypochromic (low MCV and MCH) in patients with IDA, whereas in ACD the anemia is more likely to be normocytic and normochromic [25]. Macrocytic anemia can be observed in association with vitamin B12 or folic acid deficiency, as a consequence of IBD therapy or due to increased red-cells turn-over [1]. Concerning vitamin B12 status, it can be measured by either serum B12 levels or more accurately by MMA and homocysteine levels [1]. Indeed, serum concentration of homocysteine as well as serum concentrations of MMA are elevated in vitamin B12 deficiency, whereas increased homocysteine indicates folate deficiency [51–53]. It is also known that conventional vitamin B12 testing involves measuring total serum B12 levels. The total B 12 consists of 70–90% metabolically inert haptocorrin (HC) bound B12 (HC-B12-transcobalamin) and 6–20% biologicall active transcobalamin II (active B12) [54,55]. Active B12 testing offers potential advantages in detecting early or functional B12 deficiency, as it provides insights into the availability of B12 at the cellular level. However, the clinical significance of active B12 as a standalone test is still under investigation, and more research is needed to establish its role

in clinical practice [54]. The reticulocyte count should be considered (Fig. 1). Low or 'normal' reticulocytes indicate an inability to adequately respond to anemia due to inappropriate erythropoiesis or primary bone marrow disease [11,56]. Increased of reticulocyte counts indicates red cells' production and thus rule out deficiencies. Microcytosis and macrocytosis in some situations co-exist, so RDW may help as an indicator of ID *(eg. usually elevated in IDA and normal in ACD)* [18,56]. As noted in the definition section, assessment of serum ferritin is essential to distinguish IDA from ACD. It represents the best indicator of iron stores in the body and an acute phase reactant, which can be elevated in patients with acute or chronic inflammation, malignancy, liver or tissue damage. The determination of the concentration of soluble transferrin receptor (sTfR) may also be particularly useful. sTfR is released in the plasma and its concentration is directly proportional to the total body mass of cellular transferrin receptor [18,57-59]. sTfR is elevated in plasma in situations of increased bone marrow iron requirement, both in active erythropoietic activity and in ID (true or functional). In the presence of inflammation (with normal or elevated ferritin), elevation of sTfR is therefore a good indicator of iron-deficient erythropoiesis and IDA. The lack of standardization, however, cannot recommend its widespread use in clinical practice. Hepcidin and pro-hepcidin are regulators of iron metabolism regulators, responsible for adjusting the amount of serum iron according to the body's needs. The limited amount of data does not allow to recommend their use in the clinical practice [60,61]. Other markers, such as red blood cell size factor, percentage of hypochromic red cells, and Hb concentration of reticulocytes, may be useful markers to distinguish between IDA and ACD [1,61]. When the underlying cause of anemia cannot be established, further tests may be needed, including serum concentrations of vitamin B12, folic acid, haptoglobin, lactate dehydrogenase, creatinine, and urea, as well as Hb electrophoresis and peripheral blood smear [15]. If the cause of anemia remains unclear upon more extensive workup, consultation with a pediatric hematologist is recommended [12,14].

3. Iron deficiency anemia

3.1. Diet and oral supplementation

Q7. *What is the role of diet in the prevention and treatment of anemia in children with IBD?*

Recommendation:

3.1.1. A balanced diet with a variety of iron-rich foods should be recommended to all children with IBD

[weak recommendation, low quality of evidence] [Vote result: Agree: 85 %, neutral: 5 %, disagree: 10 %]

Practice points:

- Before starting oral iron therapy, a nutritional assessment is strongly suggested.
- Foods of animal origin such as red meat, turkey, chicken and fish should be preferred due to higher levels of heme iron
- Antioxidants, such as ascorbic acid, citrus fruit, or vegetable juice can improve the iron absorption.

Summary of evidence

The goal of the nutritional intervention in children with IBD is to improve iron absorption through careful food matching while addressing nutritional management for optimization of growth [11]. The best source of dietary iron is "heme iron" found in high concentrations in animal sources with a bioavailability of about 20%, while "non-heme iron" is available from mostly plant-based dietary source, although with a lower bioavailability of about 5%. It is also important to consider that simple dietary modifications such as pairing non-heme iron sources with foods high in ascorbic acid, such as citrus fruits or vegetable juice, can lead to increased iron absorption [62]. Conversely, soy, cereals, or dietary fibers, animal proteins like milk, egg, tannins in coffee, tea or wine, oxalate in spinach, rhubarb or cacao, and phosphate in beverages sodas have been described as inhibitors of non-heme iron absorption [63]. However, changing dietary habits may not be readily accepted by patients and families, due to concerns about exacerbating abdominal symptoms [22]. Indeed, in children with IBD, active disease often leads to a decrease in appetite due to the onset of abdominal symptoms [64] and the avoidance of certain iron-rich foods, such as legumes or red meat, resulting in limited intake of oral dietary iron [22].

Q8. What is the indication for oral replacement in children with IBD and anemia?

Recommendation:

3.1.2. Oral iron therapy may be recommended for inactive disease and mild to moderate anemia, depending on age

[strong recommendation, moderate quality of evidence] [Vote result: Agree: 100 %, neutral: 0 %, disagree: 0 %]

Practice point:

- Although the optimal dose of oral iron in pediatric IBD has still not been established, 3–6 mg/kg should be suggested according to the general pediatric population anemia treatment.

Summary of evidence

Once having provided adequate control of disease activity and optimized dietary iron intake, the next step in case of persistence of IDA and no evidence of systemic inflammation is represented by iron supplementation [11]. Indeed, it is well-known that in patients with active inflammation, release of hepcidin in response to IL-6 and IL-1b causes lower iron availability and reduced intestinal absorption of oral iron [60,65,66]. According to the WHO definition of anemia, in mild anemia (Hb>10 g/dL) and/or quiescent disease, oral iron should be tried first [13]. The efficacy of oral iron supplementation in patients with mild anemia has been thoroughly evaluated in adult studies [67–72]. In a systematic review including 2906 adult IBD patients with mild anemia, Nielsen et al. reported no significant difference in terms of Hb concentrations, when comparing patients treated with oral iron supplementation with those undergoing intravenous (IV) iron at short-term follow-up [73]. Nevertheless, ferritin levels were significantly increased in the IV group [71,74,75]. However, few pediatric studies have been published on this issue [68,76]. In a recent prospective, controlled, open-label trial, Rampton et al. found that a high CRP was associated with poor response, whereas lower baseline Hb was associated with better results following oral iron therapy [77]. They also showed that oral iron supplementation did not increase disease activity in adolescents and adults with IBD over a 6-week period. Therefore, oral iron supplementation can be used in children and adolescents with milder anemia and inactive disease. Although the optimal dose of oral iron has still not been established, the recommended dose in children with IBD and IDA is 3–6 mg/kg, up to a maximum of 100 mg elemental iron per day, taken on an empty stomach in divided doses [1,78,79].

Q9. What products should be used for oral replacement in children with IBD?

Recommendation:

3.1.3. Ferrous iron products are recommended due to their better bioavailability over the iron-containing formulation

[strong recommendation, moderate quality of evidence] [Vote result: Agree: 95 %, neutral: 5 %, disagree: 0 %]

Practice points:

- Oral iron supplements are available as divalent (ferrous) salts or trivalent (ferric) in different formulations.
- The most commonly used preparations are ferrous sulfate, ferrous gluconate, and ferrous fumarate, which vary in the amount of elemental iron they contain.

Summary of evidence

Of the many oral formulations of iron, iron sulfate is the most widely used, while alternative effective formulations are iron gluconate and iron fumarate. All contain the ferrous iron form (divalent Fe^{2+}), which has a better bioavailability than ferric-containing formulations (trivalent Fe^{3+}). The iron salts in oral iron products vary in terms of the amount of elemental iron they contain. The elemental iron content is 33%, 20% and 11.6% in ferrous fumarate, ferrous sulfate and ferrous gluconate, respectively. Ferrous fumarate is only available in tablet form, whereas ferrous sulfate, ferrous gluconate, and iron polysaccharide complex are available in both tablet and liquid preparations, which are generally preferred in younger patients ([11,80]). More recently, a novel oral formulation of iron, ferric maltol, consisting of a single ferric ion (Fe^{3+}) chelated with high affinity for three maltol molecules, has been shown to be safe, effective and well-tolerated in patients with IDA and IBD, who had reported poor tolerance to other oral ferrous preparations [81].

Q10. What are the risks of oral iron products?

Statement:

3.1.4. Oral iron replacement is often associated with intolerance (nausea, abdominal pain, and constipation) and subsequent non-adherence

[low quality of evidence] [Vote result: Agree: 85 %, neutral: 10 %, disagree: 5 %]

Recommendation:

3.1.5. Due to the potential increase of intestinal inflammation, the risks and benefits of oral iron therapy should be carefully weighed in children with IBD

[strong recommendation, low quality of evidence] [Vote result: Agree: 90 %, neutral: 10 %, disagree: 0 %]

Practice point:

- Before starting oral iron therapy, a careful benefit/risk assessment, including information on possible side effects, should be considered and discussed with the family to improve overall adherence.

Summary of evidence

Oral supplement formulations have the relative advantage of being readily available and less expensive than parenteral products [82]. However, concerns exist regarding their well-documented gastrointestinal side effects [83] and the possibility of adding a burden of symptoms beyond those IBD related. Indeed, the intolerance rate is a frequent finding, leading to discontinuation in up to 50% of patients [84]. Several side effects have been reported for oral iron treatment, including nausea, vomiting, constipation, and metallic taste in up to 51% of patients [85]. While not severe, the side effects are often disturbing for patients and families. Liquid preparations of iron can occasionally cause grey of the teeth or gums. This effect is usually temporary and can be avoided or minimized by administering the iron with a syringe directed towards the back of the mouth and/or brushing the child's teeth or rinsing the mouth with water after administration of the drops. Although oral iron may cause dark stools, it does not produce false positive results on occult blood tests. Despite their gastrointestinal symptoms, oral supplementation with iron formulations may potentially negatively impact intestinal inflammation [86,87]. Indeed, studies in animal models of IBD have shown that luminal iron may exacerbate disease activity [88,89]. Unabsorbed iron is exposed to the ulcerated intestinal surface and can generate toxic free radicals and reactive oxygen species, which can directly affect gut epithelial integrity via the promotion of redox stress [3]. Oral formulations have also been associated with alterations of the gut microbiota [90]. An increase in unabsorbed intraluminal iron in the gut could therefore favor the growth of opportunistic pathogens over species beneficial for maintaining the mucosal barrier such as lactobacilli, which do not require iron, as reported in recent studies [90]. Perhaps the most important evidence that oral iron may have a negative impact on gut microbiota composition comes from studies in infants and children in Kenya and other areas of Africa, where increases in enterobacteria and decreases in lactobacilli were associated with increased stool levels of calprotectin were found after 6 months of ingestion of iron-fortified biscuits. [86,91]. Conversely, Rampton et al., as described above, reported in a 6-week study that there was no suggestion of an oral iron-induced increase in disease activity-based symptom scores, CRP or fecal calprotectin [77]. These results indicate that the pro-inflammatory effects of oral iron, acting as an oxidant and/or by modifying the gut microbiome, are not evident within 6 weeks of treatment [86,91,92]. This potential warning may therefore apply to patients who require prolonged or repeated intake of oral iron. To date, only 1 study has investigated the impact of oral iron on the composition of the gut microbiota in humans with IBD. In 2017, Lee et al. documented shifts in the metabolome, gut microbiota composition and diversity with different impact based on route of administration (oral vs IV iron) [90]. The shifts were more pronounced in subjects with IBD (especially CD) receiving oral iron, regardless of underlying disease activity, as compared with subjects without underlying inflammation [22].

Q11. How and when should we assess the response to oral iron?

Recommendation:

3.1.6. Response to iron supplementation should be assessed after 4 weeks of therapy

[strong recommendation, low quality of evidence] [Vote result: Agree: 90 %, neutral: 10 %, disagree: 0 %]

Practice points:

- After 4 weeks, an increase in Hb of 2 g/dL should be expected in responding patients.
- The recommended duration of oral iron therapy is 2–3 months.

Summary of evidence

The duration of the treatment must be adapted to achieve normalization of Hb levels, MCV, and reticulocyte counts, but also to restore iron stores [11]. Response to iron supplementation can be assessed with Hb levels after 2–4 weeks of 1–2 g/dL or, even earlier, with an increase in reticulocyte count, which is observed in 4 days (maximal response at 7–10 days). Once Hb has normalized, oral therapy should continue for approximately 3 more months to replenish iron stores ([11,14, 93,94])

3.2. Intravenous treatment

What are the indications for intravenous iron replacement in children with IBD and anemia?

Recommendation:

3.2.1. Intravenous iron replacement is recommended as a first-line treatment in patients with active IBD and/or moderate-to-severe anemia and in patients with mild-to-moderate anemia and previous intolerance to oral iron

[strong recommendation, high quality of evidence] [Vote result: Agree: 100 %, neutral: 0 %, disagree: 0 %]

Practice point:

– The dose required for IV iron replacement should be based on baseline Hb level and body weight (> 35 Kg). The traditional Ganzoni formula can be used for patients <35 Kg.

Summary of evidence

In patients with active disease, oral iron therapy may not be as effective due to poor absorption and iron entrapment in enterocytes resulting from elevated hepcidin levels combined with gastrointestinal intolerance. Therefore, intravenous therapy is preferred [11]. IV iron is more effective, shows a more rapid response, and is better tolerated than oral iron [7,67,74,75,95-101]. Compared with oral administration, IV iron increases Hb levels and iron storage and improves quality of life more rapidly but not always more rapidly [7,9,70,72,74,75]. The optimal dosing strategy for IV iron compounds depends on the type of preparation, the body weight of the patient and the Hb concentration. The amount of iron needed to correct the Hb can be calculated using the Ganzoni equation [102], often regarded as the gold standard, although this formula may underestimate the iron needed when using a target Hb of 13 g/dL and an iron stock of 500 mg to determine individual iron deficiencies [70]. Because this formula is inconvenient in clinical practice [67,70], simpler schemes for estimating total iron requirements have been published [1], including a simple scheme for predicting individual iron requirements for ferric carboxymaltose that can be used for dosing in clinical practice other intravenous iron preparations [95].

Q13. What products should we use for intravenous iron replacement in children with IBD?

Recommendation:

3.2.2. Ferric carboxymaltose (FCM) should be considered as the first-line treatment in the management of moderate to severe anemia in children≥14 years

[strong recommendation, high quality of evidence] [Vote result: Agree: 80 %, neutral: 10 %, disagree: 10 %]

Practice Points:

– The IV iron formulations approved and available for use in pediatric age are low-molecular-weight iron dextran (LMW-ID), iron sucrose (IS), ferric gluconate (FG) and ferric carboxymaltose (FCM).
– Although unlicensed in children aged < 14 years in Europe, FCM may be considered in the treatment of severe anemia in symptomatic children≤14 years to reduce the risk of blood transfusions.

Summary of evidence

All IV iron products are iron-carbohydrate complexes and consist of colloids or spherical iron-carbohydrate nanoparticles. The size and composition of the carbohydrate shell varies between products and probably contributes to the different side effect profiles of the individual active ingredients [11]. In addition to oral iron compounds, several IV formulations are available as treatment options for IDA in patients with IBD. Whereas, historically, high-molecular-weight IV iron compounds were burdened with a significant rate of side effects and thus underused due to safety concerns, the introduction of low-molecular-weight formulations has led to a significant decrease in adverse effects [103]. LMW-ID, FG and IS, as representatives of the 2nd generation, are more efficient with fewer side effects; however, they are not as stable complexes as representatives of third-generation preparations; consequently, they can only be administered in low doses, and therefore require frequent visits [104–108]. Third generation parenteral iron formulations have advantages in management in daily practice, as they offer comparably good safety profiles, high complex stability and thus the possibility of rapid application of high doses of iron up to the total cumulative dose. Furthermore, no test doses are needed with these preparations, which also simplifies their use [109]. FCM is a relatively new iron formulation currently approved in Europe for the correction of ID in adults and children over 14 years old ([12,110-113]). Differently, the drug is approved for pediatric patients of 1 year of age and older [114]. More recently, Cococcioni et al. retrospectively reviewed the charts of all pediatric patients with IBD receiving FCM infusions for IDA between July 2013 and May 2018 at two tertiary care pediatric and adolescent IBD centers [115]. One hundred and twenty-eight patients were identified, 81 (63.3%) were <14 years,10 (7.8%) <6 years. Eighty-three children (64.8%) received one infusion, whilst 45 (35.2%) repeated infusions. A significant increase in Hb, iron level and ferritin was observed 4–6 and 12 weeks after the infusion. The increase in Hb did not correlate with disease severity. Low baseline iron was the main predicting factor for repeated infusions ($p < 0.05$). Three patients reported infusion reactions, none was <6 years, suggesting that IV FCM has a good safety profile, including children younger than 6 years [115]. Ferumoxytol has been approved by FDA for use in adults since 2009 but has been used off-label in pediatric patients, but only a few reports are available on the use of ferumoxytol in children [116].

Q14. What is the safety of intravenous iron products?

Practice points:

- All IV iron preparations are relatively safe, but carry a small risk of adverse reactions, which can be life-threatening if not treated promptly.
– In order to reduce the risks related to IV iron infusions all the following minimization measures should be adopted: 1) Monitor the patient during and 30 min after the infusion by healthcare professionals with experience in the management of anaphylaxis; 2) To have the prompt availability of resuscitation equipment; 3) To carefully balance the risk/benefit analysis of in patients with known serious hypersensitivity and allergic reactions.

Summary of evidence

When choosing an agent to treat ID in a pediatric patient, many elements should be considered. First, it is important to assess the history of previous allergic reactions. There is some cross-reactivity between LMW-ID, IS, and FG, but not between these 3 products and ferumoxytol or FCM [117]. IV iron is also known to be associated with a high risk of anaphylactoid reactions. It is important that parenteral iron is administered by trained personnel. Emergency medications and resuscitation equipment should be available during these infusions. Iron infusions should be used with caution in patients with severe allergies and asthma, active se-

vere inflammation or sepsis, systemic mastocytosis, first trimester of pregnancy, current therapy with beta blockers or angiotensin converting enzyme inhibitor, severe cardiac or respiratory disease and conditions associated with iron overload [118]. In a recent meta-analysis of mainly adults and older teenagers (n = 1143 patients), Askan et al. observed that Hb response and the tolerability were mostly superior with IV iron compared with oral iron therapy [119]. They also noted response rates of 79%, 68%, and 42% with FCM, IS, and LMW-ID, respectively. Of the 543 patients treated with FCM, 12% experienced adverse events, including transient increase in liver enzymes (2.2%), headaches (1.7%), hypophosphatemia (1.7%), and hyperferritinemia (1.3%). Among 471 patients who received IS, 15.3% experienced adverse events, with burning at the site of venipuncture (1.5%) being the most commonly observed. Of the 83 patients treated with LMW-ID, 12% experienced adverse events, of which nausea and anaphylactoid reactions (3.6%) were the most common. One serious drug-related adverse event (SAE) was noted with FCM (pulmonary embolism), and another possible SAE with IS (thrombocytopenia) [111]. Although studies in adults have shown a low risk of allergic reaction to FCM, a severe and persistent hypophosphatemia has consistently been described [120,121]. Conversely, although there are evidences on the use of FCM in pediatric IBD [110–112], no data are available on the incidence of hypophosphatemia associated with FCM treatment. Cococcioni et al. in their cohort of children with IBD and IDA reported that 25 of 128 children had low post-infusion serum phosphate (3 children < 6 years) and two children developed severe hypophosphatemia [115]. Therefore, due to the high prevalence of post-infusion hypophosphatemia, serum phosphate monitoring should be routinely performed in all children receiving IV FCM in order to prevent avoidable complications [115]. These may occur within 2 months after an infusion and can present with pain, nausea, or asthenia. Rarely in severe cases, muscle weakness, rhabdomyolysis, hemolytic anemia, or cardiac dysrhythmias may occur [11]. A recent randomized, multicenter, double-blind trial comparing FCM with ferumoxytol in about 2000 adult patients with IDA of any etiology found them comparable in terms of efficacy and adverse events. Patients receiving FCM, however, had a 38.7% incidence of significant hypophosphatemia (<2.0 mg/dL). They also noted a comparable incidence of other adverse events in 3.5% of the patients in both study arms, including headache, nausea, dizziness, and fatigue [122].

Q15. How and when should we assess the response to IV iron?

Recommendations:

3.2.3. A CBC including reticulocytes should be performed after 2–4 days

[strong recommendation, low quality of evidence] [Vote result: Agree: 85 %, neutral: 10 %, disagree: 5 %]

3.2.4. Evaluation of long-term response to iv iron therapy should be performed within 4 weeks and up to 12 weeks after treatment

[strong recommendation, low quality of evidence] [Vote result: Agree: 100%, neutral: 0%, disagree: 0%]

Practice points:

- After 4 days an increase of reticulocytes should be expected
- An IV replacement goal of achieving ferritin levels up to 400 µg/L is more likely to prevent recurrence of anemia.

Summary of evidence

Response to IV iron supplementation usually occurs within 4 – 6 weeks of treatment. Hb levels help confirming correction of anemia. Cococcioni et al., in agreement with other previous studies, reported the significant improvement from baseline in all hematinic indices both 4–6 weeks and 12 weeks after FCM infusion in all 128 patients [50,115]. After 2–4 days, a CBC with reticulocytes should be obtained and an increase in reticulocytes should be expected. According to ECCO guidelines, serum ferritin levels >400 µg/L prevent recurrence of ID, suggesting that this value may be an indicator of adequate iron stores ([1,96,123]).

4. Other types of anemia

Q16. Which is the treatment of anemia of chronic disease?

Recommendation:

4.1. In the presence of anemia of chronic disease optimization of IBD treatment is strongly recommended

[strong recommendation, High quality of evidence] [Vote result: Agree: 100 %, neutral: 0 %, disagree: 0 %]

Practice points:

- Anemia of chronic disease should be suspected in the presence of active disease.
- In the presence of ACD, any anemia treatment should be preceded by optimization of IBD treatment.

Summary of evidence

ACD indicates active disease. Inflammatory markers may not always reflect underlying disease activity and careful clinical, radiographic, or endoscopic reassessment of disease status may be required [11]. The use of biological agents, especially anti-tumor necrosis factor (TNF-α) inhibitors, may be helpful in optimizing therapy in the presence of active disease. In IBD patients requiring infliximab, anti-TNF-α improved anemia through the control of inflammation and disease activity, as suggested by the combined reduction of ESR, serum ferritin, CRP. Bergamaschi et al. described an increase in serum Epo levels in patients successfully treated with anti-TNF-α, suggesting that infliximab itself may improve erythropoietin (EPO) production and bone marrow stimulation in responding patients [30]. On the other hand Infliximab induces mucosal healing and a reduction of blood lost through mucosal ulcers [30]. These data are confirmed in other chronic diseases such as ankylosing spondylitis or rheumatoid arthritis, where infliximab has been shown to lead to improvement in anemia, regardless of disease activity and duration treatment when compared with placebo [124,125].

Q17. Which is the treatment of Vitamin B12/folic acid Deficiency Anemia in children with IBD?

Recommendation:

4.2. Intramuscular vitamin B12 supplementation is recommended in case of vitamin B12 deficiency anemia

[strong recommendation, low quality of evidence] [Vote result: Agree: 80 %, neutral: 5 %, disagree: 15 %]

Practice Points

- Standard initial therapy with B12 for patients (regardless of age and weight) with macrocytic anemia without clinical involvement is 250 micrograms-1000 mcg intramuscularly three times a week for 2 weeks, followed by 250 micrograms weekly until blood count is normal, and then 1 mcg every 3 months.
- In case of terminal ileal resection >20 cm children need lifelong intramuscular B12 replacement.

– The optimal dosage of folate supplementation has not been established although a daily dose of 1 mg or a weekly dose of 5 mg appears to be sufficient.

Summary of evidence

All children with IBD should have a dietary assessment at baseline. Patients with clinical deficiency should be treated with scheduled intramuscular injections [126,127]. The dose, the duration and the frequency of treatment vary according to the clinical involvement. Hematologic response is rapid, with an increase in the reticulocyte count in 1 week and correction of megaloblastic anemia in 6 to 8 weeks. Controversy still surrounds the benefits and efficacy of oral therapy [128,129]. Folate deficiency appears to be infrequent in children with CD [130]. According to European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) recommendations, children should receive additional folic acid supplementation (1 mg daily or 5 mg weekly) during treatment with MTX, as it acts by inhibiting cellular folate uptake [126,131].

Q18. What is the treatment of drug induced anemia?

Recommendation:

4.3. Drug doses adjustment or discontinuation may be considered by carefully balancing the anemia and the severity of the IBD

[strong recommendation, moderate quality of evidence] Vote result: Agree: 100 %, neutral: 0 %, disagree: 0 %]

Practice points

– Determination of thiopurine S-methyltransferase genotype is suggested to identify patients at risk for myelosuppression.
– In children with IBD treated with thiopurines, evaluation of 6-thioguanine and 6-methylmercaptopurine may help reducing myelosuppression

Summary of evidence

Sulfasalazine, MTX and thiopurine analogs, such as azathioprine and 6-mercaptopurine, may be associated with bone marrow suppression, hemolysis or direct myelotoxicity. Drug doses adjustment or discontinuation should be made by balancing the risk/benefit of disease recurrence and drug toxicity. In IBD children receiving thiopurines, thiopurine methyltransferase (TPMT) assay (either genotype or phenotype) is encouraged as a mean to predict and prevent life-threatening leukopenia. Although the TPMT genotype/phenotype correlation is high, it is not completely reliable. For this reason, periodic blood count monitoring, as well as monitoring of liver and pancreas enzyme, remains essential throughout the duration of thiopurine therapy [1,27,132,133].

4.4. Autoimmune anemia

Autoimmune hemolytic anemia (AIHA) is a rare complication of IBD, due to the production of cross-reactive anti erythrocyte-antibodies [134,135]. Corticosteroids (metylprednisolone 1–6 mg/Kg/day) are considered first-line therapy and often cause remission of hemolysis along with IBD immunomodulator treatment and splenectomy has been used for patients with refractory AIHA [136–138]. Colectomy performed for fulminant colitis has also been reported to be beneficial for AIHA [139]. In addition, one case reports the efficacy of autologous hematopoietic stem cell transplantation and another describes the use of vedolizumab in a patient with chronic pouchitis with pouch inflammation and AIHA [140,141]. Further studies are needed for the long-term follow up and pathogenesis of this association.

Practice points

– AIHA is a rare complication of IBD and resolves with control of the disease.
– Corticosteroids are the first-line therapy of autoimmune hemolytic anemia associated with IBD, but other immunosuppressants have also produced beneficial effects. In several cases, AIHA remission was induced by curative surgical resection for IBD.

5. Refractory anemia

Q19. What is the definition of refractory anemia?

Statements:

5.1. Refractory anemia is defined by an inadequate response to optimized iron therapy

[low quality of evidence] [Vote result: Agree: 100 %, neutral: 0 %, disagree: 0 %]

5.2. In case of refractory anemia, persistent intestinal disease activity should be suspected

(low quality of evidence) [Vote result: Agree: 100 %, neutral: 0 %, disagree: 0 %]

Practice points:

– Retreatment should be considered for patients with anemia recurrence (serum ferritin <100 µg/L or Hb below the lower limit of normal for age and gender).
– There is insufficient evidence to recommend oral or IV iron prophylactic use to prevent anemia recurrence in IBD children.

Summary of evidence

Anemia in children with IBD should respond to iron replacement therapy along with treatment of IBD. It is important to ensure adequate follow-up after treatment for anemia, as up to 50% of treated patients may experience a recurrence within the following year. There is a good correlation between the extent and activity of bowel disease on the one hand and the extent of blood loss and the severity of anemia on the other [142]. Therefore, an important measure for the prevention of anemia recurrence is the treatment of the underlying disease [3,89]. As IDA recurs frequently and rapidly, iron maintenance therapy can prevent the anemia from recurring. The FERGImain study introduced the concept of a “proactive” approach to the management of anemia through the administration of FCM, instead of the traditional “watch and wait” strategy [96]. This randomized, open-label, multicenter study demonstrated the superiority of a novel fixed-dose FCM regimen over individually calculated IS doses in, 240 and 235 patients, respectively, with IBD and IDA. The simpler FCM-based dosing regimen showed better efficacy and compliance, as well as a good safety profile, than the IS dose regimen calculated by Ganzoni formula. According to this approach and the ECCO consensus, preventive anemia treatment with IV iron should be initiated as soon as serum ferritin falls below 100 µg/L or Hb drops below 12 or 13 g/dL (according to gender) [1,50]. However, there are no pediatric studies on the efficacy of oral or IV iron in prevention of ID or IDA in pediatric IBD. Up to date the pediatric approach largely relies in controlling the inflammatory activity of the disease, waiting for correction of anemia if the Hb or ferritin levels drop below the normal range. A proactive approach should be considered as aggressive instead of a watchful one. Indeed, a preventive oral iron supplementation could induce well-documented gastrointestinal side effects and a burden

of symptoms beyond those IBD related. Furthermore, a preventive IV iron treatment might add the need of peripheral venous cannula insertion and the risks related to IV iron infusions. Therefore, this watchful behaviour shows more risks than benefits and finds support in the lacking pediatrics studies.

Q20. When should erythropoiesis-stimulating agents be considered in IBD patients with refractory anemia?

Recommendation:

5.3. There is insufficient evidence to recommend the routine use of erythropoiesis-stimulating agents in the treatment of refractory anemia in children with IBD

[strong recommendation, low quality of evidence] [Vote result: Agree: 100 %, neutral: 0 %, disagree: 0 %]

Practice point:

– Selected children with anemia due to chronic disease who do not respond adequately to intravenous iron despite optimized IBD therapy may be considered for treatment with erythropoiesis-stimulating agents.

Summary of evidence

Optimization of IBD treatment should always precede any erythropoiesis-stimulating agents. In IBD patients requiring anti-TNF-α treatment, response to therapy has been shown to improve erythropoiesis [30] by significantly increasing serum EPO and sTFR levels [143]. In 2015 ECCO guidelines recommended the use of erythropoiesis-stimulating agents (EPO, darbopoietin) in patients with IBD and anemia who do not satisfactorily respond to IV iron therapy [1]. Studies in adults with IBD have shown treatment responses with increase in Hb levels and improvement in quality of life [144–148], but limited data are available on the use of EPO in children with IBD.

Q21. What are the indications for blood transfusion in IBD patients?

Recommendation:

5.4. Blood transfusion should not be solely based on the HB level, but also on a careful assessment of the child's clinical condition

[strong recommendation, low quality of evidence] [Vote result: Agree: 100 %, neutral: 0 %, disagree: 0 %]

Practice point:

– Blood transfusion should be considered when Hb levels are less than 7 g/dL or greater and symptoms or concomitant risk factors are present (eg, acute major bleeding).

Summary of evidence

Blood transfusions have become less frequent after the introduction of parenteral iron [1,11]. In children red blood cell transfusion is suggested when Hb falls below 7 to 8 g/dl [11]. Various factors other than Hb value must be taken into consideration including the general condition and stability of the patient, vital signs, ongoing blood loss, and rapidity of development of anemia [11]. Blood transfusion should be not given if Hb values are 10 g/dl or above and it is not a substitute for treatment of anemia with iron supplementation [149–151]. It is important to understand that IBD patients have a substantially increased risk of transfusion-induced red cell alloimmunization (more than 10% of young patients). When blood transfusion is necessary, extensive phenotype matching of red cell concentrates appears advisable to prevent alloantibody induction and their potentially fatal complications [152].

Summary of statements

1.2. The main types of anemia in IBD children are iron deficiency anemia, anemia of chronic disease and anemia of mixed origin.
1.3. Anemia is the most frequent extra-intestinal manifestation of pediatric IBD, although its incidence has not been fully established.
1.4. Children with IBD have a higher risk of anemia than the general population and adult patients with IBD.
1.5. Iron deficiency anemia is the most common form of anemia that occurs in IBD.
1.6. Pediatric age is an independent risk factor for anemia in IBD.
1.7. Active and severe disease is the strongest predictor for the development of anemia in IBD.
2.1. Anemia can cause a variety of symptoms depending on the type, severity, and onset.
3.1.4. Oral iron replacement is often associated with intolerance (nausea, abdominal pain, and constipation) and subsequent non-adherence.
5.1. Refractory anemia is defined by an inadequate response to optimized iron therapy.
5.2. In case of refractory anemia, persistent intestinal disease activity should be suspected.

Summary of recommendations

1.1. The definition of anemia in children with IBD should rely on currently validated WHO criteria.
2.2. Screening for anemia should be routinely performed in all children with IBD
2.3. Screening for anemia should include evaluation of hematological parameters, micronutrients deficiencies, drug toxicity, hemolysis, and inflammatory indexes.
3.1.1 A balanced diet with a variety of iron-rich foods should be recommended to all children with IBD
3.1.2. Oral iron therapy may be recommended for inactive disease and mild to moderate anemia, depending on age.
3.1.3. Ferrous iron products are recommended due to their better bioavailability over the iron-containing formulation.
3.1.4. Due to the potential increase of intestinal inflammation, the risks and benefits of oral iron therapy should be carefully weighed in children with IBD.
3.1.5. Response to iron supplementation should be assessed after 4 weeks of therapy
3.2.1. Intravenous iron replacement is recommended as a first-line treatment in patients with active IBD and/or moderate-to-severe anemia and in patients with mild-to-moderate anemia and previous intolerance to oral iron.
3.2.2. Ferric carboxymaltose (FCM) should be considered as the first-line treatment in the management of moderate to severe anemia in children$\geq$14 years.
3.2.3. A CBC including reticulocytes should be performed after 2–4 days
3.2.4. Evaluation of long-term response to IV iron therapy should be performed within 4 weeks and up to 12 weeks after treatment.
4.1. In the presence of anemia of chronic disease optimization of IBD treatment is strongly recommended.
4.2. Intramuscular vitamin B12 supplementation is recommended in case of vitamin B12 deficiency anemia.
4.3. Drug doses adjustment or discontinuation may be considered by carefully balancing the anemia and the severity of the IBD.
5.3. There is insufficient evidence to recommend the routine use of erythropoiesis-stimulating agents in the treatment of refractory anemia in children with IBD
5.4. Blood transfusion should not be solely based on the Hb level, but also on a careful assessment of the child's clinical condition.

Declaration of competing interest

The authors have no conflict of interests to declare with regards to this manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2024.02.016.

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