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POSITION STATEMENT

Approach to anaemia in gastrointestinal disease: A position paper by the ESPGHAN Gastroenterology Committee

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Abstract

Anaemia is a frequent consequence of many gastrointestinal (GI) diseases in children and it can even be the initial presenting symptom of underlying chronic GI disease. The definition of anaemia is age and gender-dependent and it can be classified based on pathophysiology, red cell morphology, and clinical presentation. Although nutritional deficiencies, including GI malabsorption of nutrients and GI bleeding, play a major role, other pathophysiologic mechanisms seen in chronic GI diseases, whether inflammatory (e.g., inflammatory bowel disease) or not (e.g., coeliac disease and dysmotility), are causing anaemia. Drugs, such as proton pump inhibitors, mesalamine, methotrexate and sulfasalazine, are also a potential cause of anaemia. Not uncommonly, due to a combination of factors, such as iron deficiency and a chronic inflammatory state, the underlying pathophysiology may be difficult to decipher and a broad diagnostic work-up is required. The goal of treatment is correction of anaemia by supplementation of iron and vitamins. The first therapeutic step is to treat the underlying cause of anaemia including bleeding control, restoration of intestinal integrity and reduction of inflammatory burden. The route of iron and vitamin supplementation is guided by the severity of anaemia.

For affiliations refer to page 539.

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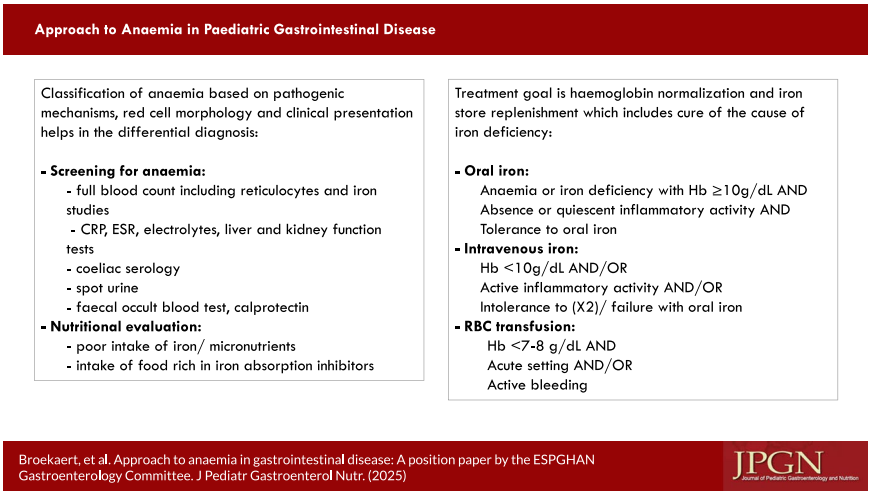

KEYWORDS

algorithm, diagnosis, therapy

1 | INTRODUCTION

Anaemia is a common consequence of many gastrointestinal (GI) disorders in children and may even be the initial presenting sign of underlying chronic GI disease. Children with anaemia are often referred to the paediatric gastroenterologist for further work-up and treatment. Anaemia associated with GI disease can substantially reduce quality of life, contribute to fatigue and may lead to hospitalisation.

With this position paper, we want to give clinical guidance regarding classification, diagnostic work-up and therapeutic management of anaemia in children with GI diseases. Therefore, statements based on evidence and if not available formulated as expert opinion were written along with recommendations and practice advice.

What is Known

- Anaemia is a common consequence of many gastrointestinal (GI) diseases in children and may even be the initial presenting sign of underlying chronic GI disease.
- There is a lack in clinical guidance on classification, diagnostic work-up and therapeutic management of anaemia in children with GI diseases.

What is New

- This is a comprehensive overview with recommendations and practice advice considering a broad differential diagnosis of anaemia allowing thorough diagnostic work-up along an algorithm especially if the initial therapeutic approach is not successful.
- A detailed array of therapeutic options weighing advantages and disadvantages as well as pitfalls along an algorithm is presented.

2 | METHODS

Databases were searched for literature on the approach to anaemia in GI disease in children until 31 December 2023, using MESH terms in PubMed, MEDLINE, EMBASE, the Cochrane Library and Scopus databases. Statements and recommendations were discussed in virtual meetings and an electronic vote was held to rate each of them using a 6-point scale (1: *strongly disagree*; 2: *quite disagree*; 3: *somewhat disagree*; 4: *somewhat agree*; 5: quite agree and 6: *strongly agree*) with an opportunity to comment. These were approved if more than 80% of the participants agreed with each (Grades 5 and 6). Statements and recommendations were, whenever possible, based on the available evidence. When evidence from paediatric studies was not available, adult data was sought. Where there was no evidence available from randomised control trials or systematic reviews, consensus among the authors was established.

3 | DEFINITION OF ANAEMIA

3.1 | Recommendation

The definition of anaemia in children with GI disease should be based on validated World Health

Organization (WHO) criteria (level of evidence [LoE]: low; strength of recommendation [SoR]: strong, voting: 100% agreement).

3.1.1 | Statement

In children with GI disease, anaemia can be classified based on pathogenic mechanisms, red cell morphology and clinical presentation (LoE: low; SoR: strong, voting: 100% agreement).

3.1.2 | Practice points

1. Vitamin B12 and/or folic acid deficiency, iron deficiency anaemia (IDA) and anaemia of chronic disease (ACD) may cause hyporegenerative anaemia.
2. IDA is diagnosed in the presence of ferritin <30 or <100 μg/L in the absence/presence of active disease, respectively.
3. ACD is multifactorial and associated with the presence of infection or inflammation.
4. Anaemia can be classified as acute or chronic according to the clinical presentation.

3.2 | Summary of evidence

Anaemia is a public health problem affecting both high- and low-income countries. Approximately one quarter of the world's population (almost 2 billion people) suffers from anaemia, with 39.8% of children <5 years of age affected, equivalent to 269 million children, and with the highest prevalence rate (60.2%) observed in children living in the African region. The WHO estimates that the global prevalence of anaemia in children aged 6–59 months in European and North American children is 20.3% and 6.1%, respectively.[1,2]

Anaemia is defined by a haemoglobin (Hb) level or red cell mass below the range considered normal for age and gender, which results in decreased oxygen-carrying capacity to the body's tissues.[3,4] The normal range of Hb varies with age, gender and race, and therefore, specified thresholds should be considered for diagnosis (Table 1). Anaemia can be classified based on pathogenesis, red cell morphology, and clinical presentation (Table 2). Regarding the pathogenic mechanisms, these are represented by inadequate production and loss of erythrocytes due to either bleeding or haemolysis. Based on these mechanisms, anaemia can be further subdivided into (a) hypo-regenerative, with a decreased bone marrow production from impaired function, decreased number of precursor cells, reduced stem cell density, or lack of nutrients; and (b) regenerative, with an appropriate bone marrow response to a reduced erythrocyte mass, characterised by increased production of erythrocytes.[6]

Hypo-regenerative anaemia can occur in aplastic anaemia, renal cell aplasia, renal failure or endocrine disorders. A disturbance in the maturation and proliferation of red blood cells (RBCs) may be caused by defective DNA synthesis, as in anaemia due to vitamin B12 and/or folic acid deficiency. In IDA, thalassaemia, and ACD, there is impaired Hb synthesis.[7] ACD is multifactorial and associated with the presence of infection, inflammation or malignancy. To understand the pathomechanism of anaemia, assessment of hepcidin levels may be very helpful. Hepcidin is an iron-regulatory hormone that inhibits iron release from cells of the reticuloendothelial system and intestinal absorption leading to hypoferraemia. An increase in hepcidin and other inflammatory cytokines, therefore, reduces the availability of iron for erythropoiesis in the bone marrow. It is usually a mild normocytic or microcytic anaemia with reticulocytopenia and with low circulating iron and low transferrin saturation, but with a normal to elevated iron storage protein ferritin.

A reduced erythrocyte mass can be the consequence of haemolytic anaemia, resulting from both intrinsic and extrinsic factors. Hereditary or acquired diseases can be the cause of intrinsic abnormalities in the structure and membrane of RBSs, such as spherocytosis and elliptocytosis, enzymatic disorders (glucose-6-phosphate dehydrogenase [G6PD] and pyruvate synthesis), sickle cell anaemia and thalassaemia. Regarding extrinsic factors of anaemia, haemolytic anaemia and thrombocytopenic purpura or disseminated intravascular coagulation represent mechanical processes with the destruction of RBCs. Furthermore, antibody-mediated destruction of RBCs can also be considered an extrinsic disorder.

The morphology of anaemia is described by RBC size, shape and colour.[5] Using this classification system, anaemias are classified as hypochromic

TABLE 1 WHO classification of anaemia according to age and severity.

Age population	Anaemia (Hb in g/dL)		
	Mild	Moderate	Severe
6 months to 5 years	10–10.9	7–9.9	<7
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	11–11.9	8–10.9	<8
Pregnant female ≥15 years	10–10.9	7–9.9	<7
Male ≥15 years	11–12.9	8–10.9	<8

Note: Adapted from reference 3.

Abbreviations: Hb, haemoglobin; WHO, World Health Organization.

TABLE 2 Classification of anaemia.

I. Classification of anaemia according to the underlying mechanism	
Anaemia due to blood loss	Acute blood loss Chronic blood loss
Anaemia due to increased rate of RBC destruction	Intrinsic: intracorpuscular abnormalities of red cells 1. Hereditary red cell membrane disorder 2. Acquired membrane defect Extrinsic: extra-corpuscular abnormalities of red cells 1. Antibody mediated 2. Mechanical trauma to red cells 3. Infection
Impaired RBC production	1. Disturbance of proliferation and differentiation of stem cells 2. Disturbance of proliferation and maturation of erythroblasts 3. Defective Hb synthesis 4. Deficient globin synthesis (thalassaemia) 5. Unknown or multiple mechanisms
II. Morphologic classification or cytometric classification of anaemia	
Normocytic normochromic anaemia (normal MCV and normal MCHC)	1. ACD 2. Anaemia due to acute haemorrhage 3. Aplastic anaemia 4. Haemolytic anaemia
Microcytic hypochromic anaemia (low MCV and low MCHC)	1. IDA 2. Thalassaemia 3. ACD
Macrocytic normochromic anaemia (high MCV and normal MCHC)	1. Vitamin B12 deficiency 2. Folic acid deficiency

Note: MCHC mean corpuscular haemoglobin concentration (adapted from Azad et al.[8]).

Abbreviations: ACD, anaemia of chronic disease; Hb, haemoglobin; IDA, iron deficiency anaemia; MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell.

microcytic anaemia (mean corpuscular volume [MCV] < 80 fL), macrocytic anaemia (MCV > 100 fL) and normocytic normochromic anaemia (MCV: 80–100 fL).[8] Main causes of microcytic anaemia include IDA, thalassaemia, and ACD, with impaired iron absorption due to tissue inflammation, such as inflammatory bowel disease (IBD).[9,10] IDA is diagnosed in the presence of ferritin <30 or <100 µg/L in the absence/presence of active disease, respectively.[11,12] Inflammation through cytokine-mediated mechanisms may trigger an increase in hepcidin and a decrease in circulating iron levels, but not ferritin, hence in the presence of biochemical and/or clinical evidence of inflammation, ACD should be diagnosed if serum ferritin levels are increased and transferrin saturation is decreased.[9,13]

Finally, anaemia can also be classified according to the form of clinical presentation as acute (usually due to bleeding or haemolysis) or chronic.[8]

4 | CAUSES OF ANAEMIA IN CHILDREN WITH GI DISEASE

4.1 | Recommendations

As there are various causes for anaemia in GI disease, a broad differential diagnosis should be considered (LoE: low; SoR: strong, voting: 100% agreement).

A dietary history is essential as nutritional deficiencies are the most common cause of anaemia (LoE: low; SoR: strong, voting: 100% agreement).

4.1.1 | Statement

The main causes of anaemia in GI disease are malnutrition, GI bleeding and inflammatory conditions (LoE: low; SoR strong, voting: 85% agreement).

4.1.2 | Practice points

1. IDA is particularly common in children below 2 years of age due to increased requirements because of rapid growth and development.
2. Low-quality diet can result in multiple micronutrient deficiencies (e.g., vitamins A, B2, B6, B12, C, D, E, folate and copper), which can have a synergistic effect on the development of anaemia.
3. High intake of cow's milk in infants can result in a poor intake of iron-rich foods and inhibition of absorption of dietary iron due to a high calcium and casein phosphopeptide content.
4. Adolescents have higher iron requirements due to rapid growth and development in both boys and girls, and due to regular blood loss during menstruation in girls.
5. As children with neurological impairment are at increased risk for anaemia, the assessment of the micronutrient status, including iron, vitamin B12 and folate should be part of the nutritional assessment.
6. In children treated with proton pump inhibitors (PPIs), anaemia can be caused by the underlying disease requiring the use of PPIs (e.g., *Helicobacter pylori* gastritis, gastroesophageal reflux) or by decreased iron absorption in the duodenum due to changed acidity.
7. Especially in children with IBD, anaemia may also be a side effect of different therapies.

4.2 | Summary of evidence

4.2.1 | Malnutrition

Nutritional deficiencies are the most common cause of anaemia.[14] The prevalence of IDA in Europe is <2% in infants under the age of 6 months, rising to about 2%–3% in infants 6–12 months and 3%–9% at 1–3 years of age.[15] The prevalence of iron deficiency (ID) without anaemia is even higher, varying between 5% and 20%.[15]

'Nutritional anaemias' are a result of insufficient intake of certain nutrients, which are needed for the synthesis of Hb and erythrocytes. The most common cause of anaemia is ID, but deficiencies of other nutrients can also result in anaemia, namely vitamins A, B2 (riboflavin), B6 (pyridoxine), B12 (cobalamin), C, D and E, folate and copper. Low quality diet can result in multiple micronutrient deficiencies, which can have a synergistic effect on the development of anaemia.

IDA is particularly common in children below 2 years of age, since their daily dietary iron requirements are high due to rapid growth and development. Moreover, complementary foods introduced in the infant's diet often have a low iron content and bioavailability, and are simultaneously rich in iron absorption inhibitors (e.g., folic acid, calcium and oxalates). Early introduction of unmodified cow's milk or unfortified formula, which are low in iron and have a low bioavailability of iron, is another common cause of anaemia in infants. In young children, high intake of cow's milk can result in poor intake of iron-rich foods and inhibition of absorption of dietary iron due to a high calcium and casein phosphopeptide content. During adolescence, iron requirements are high due to rapid growth and development in both boys and girls and even more so in girls considering regular blood loss due to menstruation.

Malnutrition, including both under- and overnutrition,[16] is associated with anaemia. In undernourished children, stunting rather than wasting is associated with anaemia.[17] There is no clear correlation between dietary intake of iron and iron status.[18,19] However, undernutrition alone (and not nutritional deficiency per se) can make children more susceptible to various conditions (e.g., parasitic infections and inflammation), which can reduce Hb levels.[17] Importantly, overnutrition is also associated with ID due to elevated levels of hepcidin.[16] In obese individuals, increased hepcidin leads to decreased expression of iron-exporter ferroportin-1, which leads to a decrease in iron absorption and plasmatic bioavailability.[16] Moreover, obesity is also associated with subclinical inflammation, which can further increase hepcidin levels.[20]

4.2.2 | Children and adolescents with neurological impairment

Undernutrition and its consequences are often present in children with neurological impairment, due to both nutritional (inadequate dietary intake because of oral motor dysfunction, gastroesophageal reflux and constipation) and non-nutritional (type and severity of underlying neurological disability, antiepileptic medication) factors. Deficiencies in iron and other micronutrients are common, occurring in about 10%–55% of these children.[21,22] Due to feeding difficulties, low energy intake is commonly reported in these children,[23] which may result in inadequate intake of all essential nutrients, including vitamins and minerals. Children with neurological impairment who are exclusively tube-fed are at increased risk of micronutrient deficiencies.[24] Volume of prescribed enteral formula, which provides adequate energy intake, is often insufficient to provide adequate amounts of micronutrients to these children.[25] Therefore, the assessment of the micronutrient status, including iron, vitamin B12 and folate should be part of the nutritional assessment of children with neurological impairment. All other micronutrient deficiencies should also be corrected and the nutritional intake should be revised by a dietitian.

4.2.3 | Pica

Pica is defined as the persistent ingestion of non-nutritive substances for more than 1 month at an age at which this behaviour is deemed inappropriate.[26] A recent study from Germany found that 12.3% of children practiced the behaviour at least once, while recurring pica behaviour was reported in 5% of patients.[27] The behaviour is most commonly observed in children with neurological disabilities, but can also occur in normally developing children. However, this condition is often overlooked by physicians and underreported by parents.[28] The most common types of pica include geophagia (clay ingestion) and amylophagia (raw starch ingestion). Complications of pica depend on the ingested material. ID is a common complication,[29,30] particularly in patients with geophagia.[31] Whether ID causes pica or pica causes ID is still a matter of debate. However, it is likely that the ingested material induces a secondary IDA either by binding iron and inhibiting its absorption and/or by adding the bulk into a child's diet already low in iron intake. Pica generally resolves on its own in children with normal cognitive function. Psychotherapy and family counselling may be required when education alone does not relieve pica.

4.2.4 | Drug-induced anaemia

Anaemia as side effect of certain drugs used in GI diseases has been reported in the literature. However, it is not listed among the most frequent causes of haematologic toxicities in children due to scarcity in the literature.

Proton pump inhibitors

ID due to the use of PPIs has been recognised for many years, although infrequently reported. Of note, anaemia can be one of the presenting symptoms in diseases requiring PPI use (*H. pylori* infection, gastroesophageal reflux, etc.). However, whilst recent studies in adults suggest it can be more frequent than previously reported (around 50% as compared to 20% reported in previous studies), no specific data are available in children.[32] Duodenal iron absorption requires the reduction of Fe^{3+} to Fe^{2+} by the duodenal apical ferrireductase STEAP3 or the duodenal cytochrome b. Dietary iron consists of both heme (32%) and non-heme (68%) iron.[32] Non-heme iron, which is mostly in the ferric (Fe^{3+}) oxidation state, is less readily absorbed and requires an acidic gastric environment to increase its bioavailability. As PPIs decrease gastric acid production, less Fe^{3+} becomes available for intestinal reduction and, hence, less ferrous iron (Fe^{2+}) is available for absorption, resulting in the development of ID.

IBD drugs

Some studies have hypothesised anaemia as a possible side effect of different therapies used in IBD, mainly in adult patients.

Mesalamine has been considered responsible for haemolytic anaemia in subjects with G6PD deficiency. This is one of the most common enzyme disorders with great variation in prevalence across geographical areas. RBCs of these individuals are very sensitive to oxidative injury, given the low amount of reduced nicotinamide adenine dinucleotide phosphate generated by the deficient enzyme. Although mesalamine compounds have been reported to be unsafe in moderate to severe G6PD deficiency by some regulatory agencies, a recent study has provided evidence that this drug, in any formulation and even at high doses (up to 4800 mg/day) is safe in this group of patients.[33]

Both sulfasalazine and methotrexate act as folate antagonists and can potentially cause megaloblastic anaemia. Concomitant therapy with folic or folinic acid (5-formyltetrahydrofolate) while on treatment with those drugs can prevent anaemia and maintain normal blood levels of folic acid.[34]

Myelosuppression can be a complication in patients treated with thiopurines (azathioprine and 6-mercaptopurine), especially in those carriers of mutations either in thiopurine S-methyltransferase (TPMT) enzyme or in the nudix hydrolase 15 (NUDT15) gene. TPMT variant alleles are associated with low enzyme activity and pronounced pharmacologic effects of thiopurines due to the high concentration of its active metabolites (thioguanine nucleotides). On the other hand, loss-of-function alleles in the NUDT15 gene are common in Asians and Hispanics and reduce the degradation of active thiopurine metabolites, also predisposing to myelosuppression.[35] Haematologic toxicity usually presents with pancytopenia, namely mild to severe leukopenia and neutropenia associated in some cases with milder anaemia and/or thrombocytopenia. Isolated anaemia in patients treated with thiopurines has not been reported. TPMT genotyping before treatment with thiopurines reduces the incidence of myelosuppression. However, some cases of myelosuppression in patients with a normal TPMT activity have been reported and other predisposition factors are suspected.[36,37]

Anaemia as a side effect of anti-tumour necrosis factor (TNF) medications (infliximab and adalimumab are approved for children with IBD) has been rarely reported. Aplastic anaemia has been described in sporadic case reports of patients treated with infliximab, but most of the cases are rheumatoid arthritis patients.[38] A single case of infliximab-induced autoimmune haemolytic anaemia in a patient with positive anti-nuclear antibody status has been reported.[39]

4.2.5 | Practice points

1. Infants with signs and symptoms of allergic proctocolitis or enterocolitis should be screened for IDA.
2. Anaemia can occur in gastroesophageal reflux disease due to chronic iron losses from erosions caused by prolonged action of acidic gastric content on the oesophageal mucosa but also because of reduced iron intake.
3. *H. pylori* gastritis in children can lead to IDA, which is unlike in adults not due to haemorrhagic lesions or gastric atrophy, but due to other factors such as competition for iron availability, the role of hepcidin or outer membrane proteins, the VacA and *sabA* gene, concomitant diseases or a poor iron intake.
4. Significant (ID) anaemia in children can be found and may be the only presenting sign in collagenous gastritis (CG), anastomotic ulcers (AUs), Meckel's diverticulum (MD), angiodysplasia, intestinal haemangiomatosis, intestinal polyps or rare genetic syndromes, such as blue rubber bleb naevus syndrome (BRBNS) and hereditary haemorrhagic telangiectasia (HHT).

4.3 | Summary of evidence

4.3.1 | GI bleeding

Cow's milk allergy

Cow's milk allergy is the most common food allergy in children younger than 3 years of age, with a reported prevalence from 0.5% to 7.5% in this age group and in <1% of children 6 years or older.[40,41] Clinically, patients may present with cutaneous, GI, respiratory and general symptoms. IDA is one of the general symptoms with a reported incidence of 1%–2.8%.[40,41] A recently published study showed that children with cow's milk allergy have a higher rate of IDA (8%) than children with other food allergies (1%), or those with no food allergies (5%, $p < 0.001$).[42] On the other hand, in children with IDA under 4 years of age, the prevalence of cow's milk allergy was reported to be 13.7%.[43] In young infants, allergic enterocolitis and allergic proctocolitis are the most common GI presentations of cow's milk allergy.[44]

Food protein-induced allergic proctocolitis (FPIAP) occurs mostly in breastfed infants (through fragments of ingested proteins excreted into the mother's milk) and presents with haematochezia. However, these infants rarely become anaemic.[40,41] Reports on the prevalence of FPIAP range widely, from 0.16% in asymptomatic children to even 64% in patients with haematochezia. FPIAP usually begins within the first weeks of life and resolves in late infancy.[40] In exclusively breastfed infants, breastfeeding should be encouraged and elimination of cow's milk in the maternal diet can be considered.

Food protein-induced enterocolitis syndrome (FPIES) is a non-IgE-mediated allergy with cow's milk protein being one of the most commonly reported triggers.[40] These infants experience emesis and watery diarrhoea after ingestion of the allergen. Chronic FPIES develops after repeated ingestion of the triggering food leading to poor weight gain or weight loss, hypoproteinaemia and anaemia (reported in 25% of patients).[45,46] Children with FPIES often require longer periods of food avoidance, but most develop tolerance by school age.[45]

Heiner syndrome is a rare food-induced hypersensitivity to cow's milk protein characterised by chronic respiratory symptoms with pulmonary infiltrates, failure to thrive, GI symptoms (vomiting and diarrhoea) and anaemia.[47] About 10% of affected children develop a severe form of the disease leading to pulmonary hemosiderosis. The symptoms usually commence before the age of 1 year but may occur up to the fifth year of life and resolve within 1–3 weeks of discontinuation of cow's milk.[48]

Gastroesophageal reflux disease

Gastroesophageal reflux disease develops when gastroesophageal reflux causes troublesome symptoms and/or complications.[49] These symptoms are present daily in more than a quarter of infants but gradually disappear by the age of 12 months. In older children, symptoms are present in >10% of children on a daily and in 25% on a monthly basis.[49] Based on the literature, 4%–13% of these children have anaemia.[50] Anaemia can occur due to chronic iron losses from erosions caused by prolonged action of acidic gastric content on the oesophageal mucosa but also because of reduced iron intake.[50] There are only a few published paediatric studies on the prevalence of anaemia in children with gastroesophageal reflux disease (indicating that 4%–13% of these children have anaemia), and only one showed a moderate correlation. Further studies are needed to confirm if there is indeed a correlation or if these are just two common unrelated conditions.[50]

Gastritis caused by H. pylori

H. pylori infections affect more than a half of the world population, but the severity and phenotype of gastric pathology depends on a complex interplay between various factors of the bacteria itself, the host, and the environment.[51] Although it is well documented that persistent *H. pylori* infection in the gastric mucosa in children can lead to IDA, the pathogenesis and specific risk factors remain poorly understood. Most children with *H. pylori*-associated anaemia do not show evidence of overt blood loss due to GI haemorrhagic lesions. Unlike adults, in *H. pylori*-infected children, gastric atrophy and intestinal metaplasia are rarely found, suggesting that impaired gastric acid secretion may not be a primary or direct cause of *H. pylori*-associated IDA. Therefore, some other possible

mechanisms have been proposed such as: competition for iron availability, the role of hepcidin, the role of outer membrane proteins (some encoding genes are involved in iron-uptake mechanisms), the VacA and *sabA* gene, concomitant diseases such as coeliac disease (CD), parasitic infection and a poor iron intake.[52]

H. pylori-*negative chronic gastritis*

Apart from *H. pylori* gastritis, other forms of gastritis (such as eosinophilic gastritis and autoimmune atrophic gastritis) may present with anaemia.[53] Clinical presentation of eosinophilic gastritis is variable, with abdominal pain as the most common symptom followed by vomiting and other symptoms including anaemia, melaena, food aversions, failure to thrive, oedema and ascites.[53]

Autoimmune atrophic gastritis is an inflammatory disease characterised by atrophy of the mucosa induced by autoantibodies against parietal cells or intrinsic factors. Several cases have been reported in children.[53] Autoimmune processes damage the parietal cells, resulting in hypochlorhydria and reduced secretion of intrinsic factors. As hydrochloric acid is essential for solubilisation and reduction of food iron, conditions critical for its normal absorption, hypochlorhydria results in iron malabsorption and IDA. Parietal cell loss, as well as antibodies against intrinsic factors, may lead to vitamin B12 deficiency and anaemia. However, pernicious anaemia typically occurs later in the disease course.[54]

Collagenous gastritis

CG is a rare disease characterised by subepithelial collagen deposition and mixed inflammatory infiltrates in the gastric mucosa.[55] A recent study from Sweden reported an incidence of childhood-onset CG of 0.25/100,000 person-years.[56] The current gold standard for the diagnosis is upper endoscopy with gastric biopsies and histopathology showing subepithelial thickening of the collagen band (>10 μm).[53] Affected children typically present with severe symptomatic IDA (fatigue, pallor, palpitations and dyspnoea) and abdominal pain, sometimes accompanied by recurrent vomiting, weight loss, nausea, diarrhoea and GI bleeding.[53,55] Anaemia can develop later in the course of the disease.[55] The mechanism of IDA remains unclear but can be attributed to the damage of dilated capillaries entrapped in the subepithelial collagen band and erosive gastritis.[53,55] A large paediatric cohort study on CG showed that 30 out of 40 (75%) of patients had anaemia and in all of them, symptoms of anaemia improved and blood counts normalised with iron supplementation. Resolution of anaemia without need for iron for at least 6 months occurred in 16% of patients (within a range of 6 months to 5.2 years after diagnosis) while the others (71%) had no anaemia with ongoing iron supplementation or had recurrence of anaemia after discontinuation or poor compliance to the treatment.[55] Other medications (PPIs, sucralfate, prednisone and budesonide) are mainly directed at symptom control, but their benefits remain unclear.[53,55] The natural history and long-term progression of CG are variable. In some cases, there is a complete resolution; however, the majority has a chronic disease pattern.[55]

Anastomotic ulcers

AUs in the GI tract can develop early after anastomotic formation until up to 28 years after initial surgery.[57] The incidence of AU is between 0.3% and 8%.[58] Besides IDA, AU can present with abdominal pain, diarrhoea, and GI bleeding, however, IDA may also be the only presenting symptom. The pathogenesis is not well understood; therefore, the therapeutic approach is variable. Antibiotics, mesalamine, sulfasalazine and immunosuppressants can be used although results in the literature are usually poor.[59] If necessary, endoscopic therapy with argon plasma coagulation of the ulcers and clipping is performed with some promising results.[60] Surgery with resection and establishing a new anastomosis must be considered if conservative methods and endoscopy are not efficient. Recurrence of AU is not uncommon even after successful surgery.

Meckel's diverticulum

MD is a quite common congenital diverticulum of the last part of the small intestine resulting from incomplete atrophy of the vitelline duct in the embryo.[61] The estimated incidence is between 0.6% and 4%. MD can be asymptomatic or can present with life-threatening conditions such as intestinal obstruction, perforation, inflammation, and severe bleeding. According to paediatric data, symptomatic MD presents mainly with obstruction (46.7%) and GI bleeding (25.3%), but also with anaemia.[62] Painless rectal bleeding is the result of acid produced from a patch of ectopic gastric mucosa at the site of the MD. Nuclear scans with TC-99m pertechnetate can visualise the MD with a specificity of 97.1%, but a lower sensitivity of 89.6%; therefore, if clinical suspicion is high the scan should be repeated.[63] The therapy is surgical: either a diverticulectomy or a segmental resection of the ileum, with the latter being preferred to ensure full resection of any ectopic gastric tissue, which is usually located in the ileum and not in the MD itself.

Angiodysplasia

Angiodysplasia (vascular ectasia) is a rare cause of GI bleeding affecting any part of the GI tract. The most commonly involved areas in children are the ascending colon and the terminal ileum.[64] Therapy depends on the severity of bleeding and recurrence of symptoms. In more than 90%, bleeding stops spontaneously, but it can recur. Argon plasma coagulation is a safe and effective therapy for symptomatic children.[65]

Intestinal haemangiomatosis

Intestinal haemangiomatosis may be part of diffuse neonatal haemangiomatosis, which is a rare and possibly life-threatening congenital disorder. Intestinal haemangiomas are more common in the small bowel and most commonly present with painless GI bleeding ranging from slowly progressive to massive or life-threatening.[66] Other manifestations include intussusception, bowel obstruction, anaemia or perforation, and congestive heart failure.[66,67] Computed tomography (CT) and magnetic resonance imaging (MRI) are non-invasive and reliable methods to diagnose haemangiomatosis.[66] In addition to colonoscopy, scintigraphy or capsule endoscopy may be useful when the bleeding focus is not detected by other exams. Propranolol has been described as an effective treatment for infantile haemangiomas, and besides surgical or endoscopic treatment, patients may respond to propranolol treatment alone.[66]

Polyps

Polyps are less common in children than in adults. In childhood, juvenile polyps typically present with painless lower GI bleeding between the age of 2 and 5 years and occur in up to 2% of children under the age of 10 years.[68] Children with a significant polyp burden, such as in juvenile polyposis and Peutz-Jeghers syndrome, may present with IDA, protein-losing enteropathy and hypoalbuminemia.[69] Most intestinal polyps in children are nonfamilial like juvenile polyps and inflammatory polyps. Hereditary polyps are part of well-described polyposis syndromes, most of which have malignant potential, including a higher possibility of extraintestinal neoplasms. The mucosa of the polyps can be erythematous and friable and can easily bleed. When the diagnosis is made with endoscopy, a polypectomy can safely be performed.

4.3.2 | GI syndromes associated with anaemia

Anaemia in children can be caused by a few rare vascular malformation syndromes, which may be considered when evaluating a child with refractory anaemia.

Blue rubber bleb naevus syndrome

BRBNS is a rare congenital syndrome (estimated incidence 1:14,000 births affecting both sexes) of venous malformations or blebs that commonly arise in the skin and GI tract, with only a few hundred cases reported. Rarely, lesions may be found in other organs, such as the liver, spleen, heart, eye, bladder, kidney, lung and central nervous system.[70–72]

Visceral involvement tends to present in early adulthood. The small bowel is the most common site of GI tract involvement; however, lesions can occur anywhere in the GI tract. As a result, patients may present with severe IDA from recurrent GI haemorrhage.[73]

Ultrasound is the initial diagnostic method of choice for visceral lesions. It can be performed endoscopically if GI venous malformations are suspected. Other diagnostic modalities include MRI, CT, barium studies, and skin biopsy. Wireless capsule video endoscopy and therapy using double-balloon enteroscopy have allowed mid-small bowel blue rubber bleb lesions to be assessed and treated effectively.[74] Pharmacologic agents have been tried with variable responses.[75] If there is significant intestinal involvement, surgical resection may be the only choice to prevent life-threatening GI haemorrhage.[76,77]

HHT (Osler–Weber–Rendu syndrome)

HHT or Osler–Weber–Rendu syndrome is a vascular disorder inherited as an autosomal dominant trait, with a variety of clinical manifestations. Clinical prevalence in the population is estimated between 1:5000 and 1:8000, with approximately 85,000 individuals affected in Europe.[78–81] Since the majority of patients are unaware of their diagnosis, HHT is likely to be underreported.[82,83]

Lesions found in HHT include arteriovenous shunts and telangiectasia. HHT develop with increasing age and are not generally present at birth. The most common problems are epistaxis, GI bleeding and IDA, along with characteristic mucocutaneous telangiectasia. Arteriovenous malformations frequently affect the liver, lungs and central nervous system. The combination of epistaxis, GI bleeding and IDA associated with characteristic telangiectasia on the lips, oral mucosa and fingertips is typical of HHT.[81,84]

Bleeding GI lesions in HHT may be accessible for local endoscopic therapy. Embolization and/or surgery may be useful for emergency control of haemorrhage from discrete lesions. This is also the preferred option for diffuse or endoscopically inaccessible severe GI bleeding. Pharmacologic treatment with bevacizumab, an antiangiogenic agent that inhibits vascular endothelial growth factor, can be useful in individuals with severe bleeding.[84,85]

4.3.3 | Practice points

1. In children with exocrine pancreatic insufficiency (EPI), the causes of anaemia can be ID, bone marrow failure or adverse events of medications.
2. In children with cystic fibrosis (CF), causes of ID are chronic inflammation due to pulmonary exacerbations, impaired dietary absorption, or increased loss via sputum, and IDA may be the initial presenting symptom in these children.

3. IDA is frequently present at initial diagnosis and may be the only manifestation of coeliac disease. It is most likely caused by malabsorption due to small bowel villous atrophy, but also GI bleeding and inflammation may play a role.
4. Children with IBD often present with IDA and co-existing ACD, and may have functional ID (FID) mimicking IDA.
5. Anaemia in children with IBD may be a biomarker of disease activity, with refractory anaemia indicating persistent inflammation, as well as a prognostic marker, as it is associated with worse patient outcomes.
6. In children with IBD, therapy with oral iron supplementation may not be successful as epithelium iron stores are saturated due to elevated hepcidin levels caused by intestinal inflammation.
7. Deficiencies due to micronutrients other than iron may contribute to anaemia in children with IBD.
8. Screening for vitamin B12 metabolism should be performed especially in Crohn's disease patients with terminal ileal disease, after resection of the terminal ileum, or with small intestinal bacterial overgrowth, and for folic acid especially in patients with extensive small intestinal disease or taking thiopurines.
9. Intestinal dysmotility, such as achalasia, gastroparesis and paediatric intestinal pseudo-obstruction (PIPO), may cause poor caloric intake resulting in IDA.

4.4 | Summary of evidence

4.4.1 | Malabsorptive causes of anaemia

In children with EPI, the causes of anaemia can be ID, bone marrow failure or even adverse events of medications.

In CF, the main cause of anaemia is ID secondary to chronic inflammation due to pulmonary exacerbations, impaired dietary absorption or increased loss via sputum. The assessment of the iron status is difficult because of inflammation, which increases ferritin levels. In adult studies, the prevalence of ID ranges from 11% to 87%.[86] In recent studies, prevalence of ID was 41.8% [87] and 44.2%,[86] and the prevalence of anaemia was 33%.[87] Factors associated with ID are female gender, age <30, presence of *Pseudomonas aeruginosa* in sputum,[86] vitamin A deficiency and moderate to severe lung disease.[87] It is of note that ID or anaemia were not associated with EPI, suggesting that iron malabsorption does not play a main role in iron metabolism.[87] In children with CF, the prevalence of ID, defined by iron levels <12 mg/L < 5 years of age or <15 mg/L > 5 years of age, was 60.4%, and anaemia, defined by Hb <2 SD according to age and sex, was 24.5%.[88]

Previously, ID could be present at diagnosis because of malnutrition. Meanwhile, newborn screening and therapeutic management have decreased the rate of malnutrition. However, severe anaemia remains a concern and can be the first symptom at diagnosis.[89] In a Turkish study, 17 out of 231 infants had severe anaemia at diagnosis; it was associated with prolonged prothrombin time and low albumin levels, but not with EPI, which also suggests that malnutrition, but not malabsorption, contributes to ID.

Healthcare providers feared that iron supplementation could potentiate pulmonary infections because iron could trigger bacterial growth and enhance the formation of *P. aeruginosa* biofilm communities. However, in a small randomised clinical trial with 22 CF adults with IDA treated with a low dose of iron (ferrous sulphate 325 mg daily for 6 weeks), iron status improved without correcting anaemia and without affecting iron sputum load, pulmonary exacerbation, and lung microbiome.[90] Thus, ID remains a concern in relatively healthy, well-nourished CF children. Finally, antibiotic treatment exposed CF patients to drug sensitivity and haemolytic anaemia.[91]

Anaemia is also present in children with other EPI conditions. In a large Italian cohort of 121 Shwachman–Diamond Syndrome children, anaemia was present at the first haematologic assessment in 4.6%, and the cumulative incidence of severe anaemia at 30 years was 20.2%.[92] Cytopenia is due to bone marrow failure. It is often intermittent or asymptomatic. Anaemia is also present in Pearson syndrome and in Johanson–Blizzard syndrome.

4.4.2 | Coeliac disease

The prevalence of anaemia in newly diagnosed CD patients ranges from 12% to 69%.[93] The aetiology of anaemia in CD is multifactorial. The major cause is malabsorption as a consequence of small bowel villous atrophy, but also GI bleeding and inflammation may play a role.[93–96] IDA refractory to iron supplementation can be the only manifestation of CD, especially in children, and it is characterised by microcytic, hypochromic anaemia with low iron and ferritin levels and elevated total iron-binding capacity. The prevalence of CD in patients with refractory IDA may reach 20%.[93] In CD, systemic inflammation is associated with increased production of inflammatory cytokines, such as interferon-gamma, TNF-α and interleukin-15, which in turn increases the hepatic production of hepcidin-inducing ACD.[95]

It is also noteworthy that CD patients with anaemia presented higher values of autoantibodies and a lower

body mass index at diagnosis compared to those without anaemia, as well as a slower histologic response to gluten-free diet (GFD), suggesting more severe disease.[97] On the other hand, even if more frequent in patients with severe mucosal atrophy, CD-associated anaemia and ID are a continuum and may already be present in children with potential CD (i.e., subjects with positive coeliac serology but normal intestinal mucosa).[98]

The main treatment consists of a GFD and iron supplementation until iron deposits are restored. It may take up to a year for Hb to normalise and up to 2 years to restore iron deposits.[93]

Deficiencies in folate and vitamin B12 are also common in CD patients and may induce anaemia. However, due to the frequent concomitance with iron malabsorption, atypical findings on the blood smear may be found instead of the classic macrocytic anaemia. Folate and vitamin B12 supplementation is recommended in these patients.[93]

4.4.3 | Inflammatory bowel disease

Anaemia is common in children with IBD and it can be considered a biomarker of disease activity. Prevalence rates are reported as high as 78% in newly diagnosed children with IBD.[99] There are several aetiologies of IDA in IBD (Table 3). IDA and ACD are the two most common types of anaemia in IBD and can often coexist. In addition, in IBD patients, FID (Table 4) can mimic IDA.[9,101] In FID, iron stores may be barely adequate, but iron is not available for erythropoiesis. This may be due to ACD, where iron release from macrophages back into the circulation is blocked due to increased hepcidin, or to erythropoiesis-stimulating agents, where the release of iron into the circulation may not be rapid enough to support erythropoiesis. The pathophysiology of anaemia in IBD is based on the dysregulation of iron homoeostasis and the pivotal role of hepcidin.[99] Limited luminal iron is absorbed from oral diet or supplements because epithelium iron stores are saturated. Therefore, in IBD, oral iron supplements are unlikely to improve blood iron status.[102]

A recent study has shown that many children with IBD suffer from anaemia and micronutrient deficiencies at diagnosis and some fail to recover after 1 year despite being in clinical remission.[103] The prevalence of deficiencies in this cohort at diagnosis and 1-year follow-up, respectively, were among others iron (56% and 27%), ferritin (39% and 27%), vitamin D (22% and 13%), vitamin A (25% and 25%), vitamin E (5% and 4%), copper (17% and 27%), vitamin B12 (2% and 5%) and RBC folate (1% and 17%). Anaemia was present in 57% and 25% at diagnosis and 1-year follow-up, respectively. Each of these micronutrients plays several roles not only in anaemia and the course of disease.[103,104] Vitamin B12 deficiency in children with IBD can be secondary to extensive terminal ileum resection, dietary restriction in vegans, intestinal inflammation, or small intestinal bacterial overgrowth. Therefore, in patients at risk for vitamin B12 or folic acid deficiency (e.g., small bowel disease or resection), both micronutrients should be monitored at least annually, or if macrocytosis is present, especially in the absence of thiopurine use.[9]

Anaemia in IBD needs to be diagnosed and managed promptly as many studies have shown that is associated with worse patient outcomes and impacts healthcare resource consumption.[105–107]

4.4.4 | Dysmotility

Achalasia

Oesophageal achalasia is a rare oesophageal motility disorder characterised by lack of oesophageal peristalsis and partial or absent lower oesophageal sphincter (LES) relaxation upon swallowing. The main pathophysiologic mechanism is represented by selective degeneration of inhibitory myenteric oesophageal neurons, which play a key role in regulating the peristalsis of the smooth muscle of the oesophageal body and LES relaxation. The aetiology of achalasia is largely unknown, although several data suggest an autoimmune-mediated process. The most common symptoms at presentation are vomiting, dysphagia, weight loss, chest pain, and regurgitation. Children are more likely to experience respiratory symptoms, such as chronic cough and recurrent respiratory infections.

Weight loss was reported in about two thirds of children with achalasia, and faltering weight in one third, both related to poor caloric intake and recurrent regurgitation of food content besides a limited amount of nutrients reaching the absorptive area of the gut. While a recent study showed that iron intake was significantly lower than in healthy controls, the serum levels were normal.[108] Although data in the literature are limited, it is expected that children with untreated achalasia and significant long-term symptoms would develop IDA.

Gastroparesis

Gastroparesis is defined as delayed gastric emptying of fluids and/or solids in the absence of a mechanical obstruction. The most common symptoms include nausea, vomiting, bloating, early satiety, abdominal pain and weight loss. Anaemia is not uncommon in gastroparesis and is related to poor oral intake due to significant foregut symptoms, such as nausea, early satiety, postprandial fullness and vomiting. IDA has been reported in approximately half of the adult population with gastroparesis (diabetic and non-diabetic) along with other nutritional deficiencies.[100] Moreover, ID was reported in 69% of adults with gastroparesis,

TABLE 3 Aetiologies of IDA in IBD.

Aetiology of IDA during active IBD	
1.	Increased excretion of iron from epithelial desquamation and active mucosal bleeding
2.	Decreased intake of dietary iron due to ongoing GI symptoms
3.	Reduced transport of iron to the blood due to high hepcidin concentration
4.	Impaired erythropoiesis as a result of inflammation or IBD medication-induced toxicity
Aetiology of IDA during quiescent disease	
1.	Inadequate iron repletion after active disease
2.	Ongoing low-grade inflammation that inhibits optimal blood iron concentrations, which contributes to the development of ACD
3.	Persistent poor intake of iron-rich foods
4.	Low intake of iron absorption-promoting foods (e.g., fruit and vegetables high in vitamin C)
5.	High dietary intake of inhibitors of iron absorption (e.g., tannins, phytic acid, high protein intake, and calcium)
6.	Concurrent micronutrient deficiency (e.g., vitamin B12, vitamin D, and folate)

Abbreviations: GI, gastrointestinal; IBD, inflammatory bowel disease; IDA, iron deficiency anaemia.

TABLE 4 Various tests used to differentiate IDA from ACD and FID.

	IDA	ACD	FID
Hb	↓	↓	↓
MCV	↓	Normal	↓ or normal
Ferritin	↓	↑	↑ or normal
Iron level (unreliable)	↓	↓	↓
Transferrin	↑	↓	↓
Transferrin saturation	↓	↓/↑	↓
sTfR	↑	↓ or normal	↑ or normal
sTfR-F	>2	<1	<2, variable
Zinc protoporphyrin	>40	<40	>40
CRP	Normal	↑	↑
Hepcidin	↓	↑	↑ or ↓
STfR-F/Chr	↑/↓	↓/↑	↓/↓

Note: Adapted from Goyal et al.[99]

Abbreviations: ACD, anaemia of chronic disease; Chr, Hb content in reticulocytes; CRP, C-reactive protein; FID, functional iron deficiency; Hb, haemoglobin; IDA, iron deficiency anaemia; MCV, mean corpuscular volume; sTfR, soluble transferrin receptor level; sTfR-F, sTfR log ferritin index.

occurring more commonly in idiopathic than diabetic gastroparesis.[109]

Paediatric intestinal pseudo-obstruction

PIPO is the most severe GI motility disorder in children and is characterised by symptoms and signs arising from the inability of the GI tract to propel its luminal content in the absence of a mechanical obstruction. PIPO can be acquired or congenital, and based on its aetiology can be classified into primary, secondary or idiopathic causes, whilst based on histopathology into neuropathies, myopathies or mesenchymopathies. The clinical manifestations of PIPO are extremely variable and determined by the age of onset (i.e., prenatal, neonatal and late-onset disease), the extent of the disease and the phase of the disease (relapse or remission). The most common symptoms include significant abdominal distension, abdominal pain, vomiting, faltering growth and inability to tolerate enteral nutrition.

Long-standing symptomatology before diagnosis of PIPO often leads to malnutrition and associated nutritional deficiencies resulting in IDA. Due to third spacing of pooling fluid in the distended bowel loop leading to unreliable weight measurement, malnutrition can be underdiagnosed. Children with PIPO receiving home parenteral nutrition are at risk of developing IDA, as this is commonly associated with home parenteral nutrition.[110] Furthermore, as many children with PIPO undergo ileostomy, the degree of diversion colitis in the disconnected segment can sometimes be significant and exacerbate anaemia.

IDA and the impact on oesophageal motility

IDA was found to be associated with a decrease in oesophageal contractions and an increase in oesophageal transit duration. The most probable mechanism is that ID leads to rapid loss of iron-dependent enzymes and mucosal degeneration.[111,112]

5 | DIAGNOSTIC APPROACH IN ANAEMIA

5.1 | Recommendations

Screening for anaemia should be performed in all children with acute and chronic GI disease at initial diagnosis and be repeated on a regular basis based on the degree of anaemia and the course of the underlying condition (LoE: low; SoR: strong, voting: 100% agreement).

5.1.1 | Statement

In chronic inflammatory GI diseases such as IBD, it is necessary to differentiate IDA from ACD and FID (LoE: low; SoR: strong, voting: 92% agreement).

5.1.2 | Practice points

1. Screening for anaemia should include evaluation of haematological parameters, iron status, inflammatory parameters, coeliac serology and stool testing for faecal occult blood and calprotectin (Table 1).
2. A nutritional evaluation includes assessment of micronutrient intake and intake of foods capable of inhibiting iron absorption (Table 1).
3. MCV as well as reticulocyte count are helpful to classify anaemia, initiate further diagnostic testing and find the GI aetiology of anaemia (Table 1).

Summary of evidence

For the diagnostic approach, it is helpful to use the classification of anaemia regarding pathogenesis (hypo-regenerative anaemia with a low reticulocyte count vs. regenerative anaemia with a normal or high reticulocyte count) and red cell morphology (microcytic vs. normocytic vs. macrocytic anaemia) (Figure 1).

Despite the availability of various tests, a single test may not distinguish IDA from ACD or FID.[113,114] Therefore, it is helpful to use a combination of tests (Table 4).

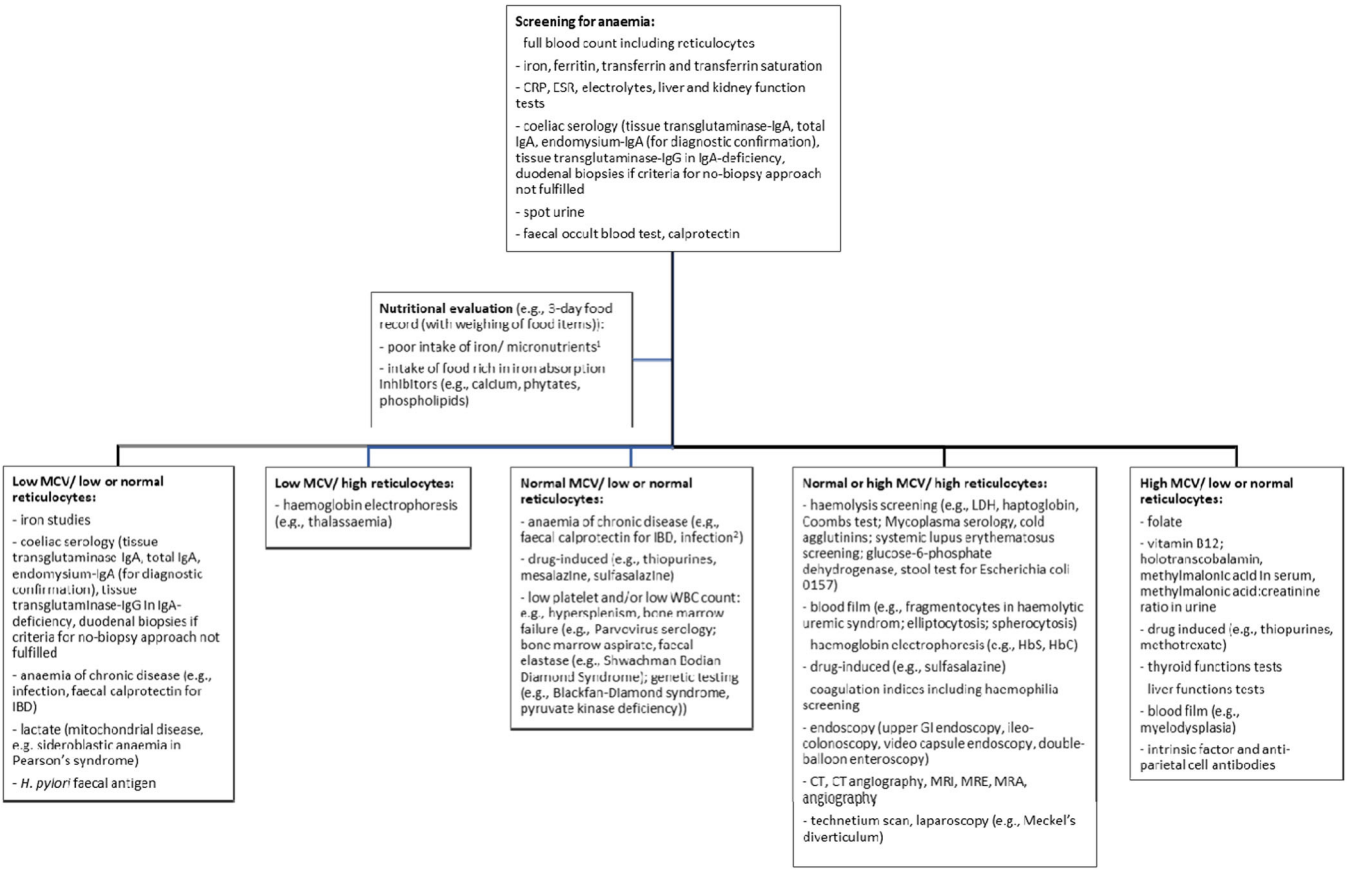

FIGURE 1 Suggested algorithm for diagnosis of anaemia in children and adolescents with GI disease. CMV, cytomegalovirus; CRP, C-reactive protein; CT, computer tomography; EBV, Epstein–Barr virus; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; IgA, immunoglobulin A; GI, gastrointestinal; *H. pylori*, *Helicobacter pylori*; HbC, haemoglobin C; HbS, haemoglobin S; LDH, lactic dehydrogenase; MCV, mean corpuscular volume; MRA, magnetic resonance angiography; MRE, magnetic resonance enterography; MRI, magnetic resonance imaging; WBC, white blood cell. 1. For example, folic acid and vitamin B12. 2. Infectious causes: giardiasis, malaria, tuberculosis, EBV and CMV.

6 | THERAPEUTIC MANAGEMENT OF ANAEMIA

6.1 | Recommendations

The treatment of anaemia in children with GI diseases should be guided by the aetiology and the severity of the condition (LoE: low; SoR: strong, voting: 100% agreement).

6.1.1 | Statements

Treatment goals are normalisation of Hb levels and replenishment of iron stores by correcting the aetiology including bleeding control, restoration of intestinal integrity, and reduction of the inflammatory burden (LoE: low; SoR: strong, voting: 100% agreement).

6.1.2 | Practice points

1. In children with mild anaemia (Hb ≥10 g/dL), and in mild or inactive inflammatory disease, IDA should be treated with a combination of iron supplementation, optimisation of dietary intake and control of disease activity.
2. In children with moderate-to-severe anaemia (Hb <10 g/dL), and/or active inflammatory activity, intolerance or inadequate response to oral iron, poor compliance, parenteral iron is indicated.
3. Erythrocyte transfusions are reserved for children with acute bleeding and a rapid drop in Hb levels <7–8 g/dL, and in clinically unstable patients.
4. Orally administered iron should be taken on an empty stomach in a mildly acidic environment such as ascorbic acid to increase GI absorption.
5. A dietary strategy to improve iron status consists of consumption of heme iron-containing foods (e.g., red meats, poultry and fish) and non-heme iron foods (e.g., fortified cereals and bread, pulses, nuts and seeds) in combination with foods high in ascorbic acid, which enhance non-heme iron absorption.
6. Phytates, polyphenols, calcium and animal protein (egg protein, milk protein and albumin) decrease GI iron absorption and should, therefore, be consumed separately from iron-containing meals.
7. Foods rich in iron (e.g., animal protein and fortified cereals) should be introduced early during complementary feeding since by 6 months of age, the infant's endogenous iron stores will have been used up.
8. Recommended dosing of oral iron in children ranges from 2 to 6 mg/kg/day, administered once a day, and should not exceed the adult recommended dose of 100 mg of elemental iron per day.
9. The duration of oral iron therapy depends on the severity of anaemia at treatment initiation and the patient's response, but usually lasts between 8 and 12 weeks.
10. Frequent GI side effects of oral iron are constipation, diarrhoea, abdominal pain, and nausea, and oral iron preparations may have an effect on the intestinal microbiome.
11. The response to oral iron therapy should be assessed after 4 weeks of treatment.
12. There are different parenteral iron formulations approved and available for children, such as iron dextran, iron sucrose, ferric gluconate, ferric carboxymaltose and ferumoxytol.
13. All parenteral iron preparations are relatively safe, but carry a small risk of adverse reactions, such as allergic reactions, which need to be treated promptly.
14. Patients having received parenteral iron should be monitored for phosphate levels as parenteral iron formulations may cause post-infusion hypophosphatemia.
15. Evaluation of response to parenteral iron therapy should be performed at 4 and 12 weeks after treatment.
16. The decision to transfuse erythrocytes should be based on assessment of the clinical condition, including the stability of the patient, ongoing blood loss and how quickly the anaemia has developed, as well as Hb levels (<7–8 g/dL).

6.2 | Summary of evidence

The treatment of anaemia in children with GI diseases is driven by the aetiology and the severity of the condition. The therapeutic goals are Hb normalisation, replenishment of iron stores and correction of vitamin deficiencies. The first step is to counteract the causative factor leading to anaemia including bleeding control, restoration of intestinal integrity, and reduction of the inflammatory burden. In mild anaemia (Hb ≥10 g/dL) and in mild or inactive disease, both IDA and ID should be treated initially with a combination of iron supplementation, dietary intake optimisation and disease activity control.[115] It should be considered that during active inflammation, oral iron therapy may be less effective due to poor absorption caused by iron entrapment in the enterocytes secondary to elevated hepcidin levels.[115] Parenteral iron is indicated in children with moderate-severe anaemia, inadequate response to oral iron treatment, poor compliance or intolerance.

Inadequate response to oral iron is defined as an increase in Hb <1 or <2 g/dL within 2 or 4 weeks of starting treatment, respectively.[10] Persistent ID after a course of oral iron or frequent recurrence of ID should also initiate a switch to parenteral iron. Oral iron intolerance is defined as the inability to tolerate at least two different oral iron

formulations. Intravenous iron should be strongly considered in those circumstances (Figure 2).

In children with severe anaemia and in patients with refractory active disease, intravenous iron should be considered as first-line treatment. RBC transfusions are reserved for acute cases with a rapid drop in Hb values (of <7–8 g/dL) and in clinically unstable patients.

6.2.1 | Dietary strategies

There are two forms of dietary iron: heme iron which is more effectively absorbed and non-heme iron which has about two thirds of the bioavailability of heme iron.[116] Foods containing heme iron include red meats, poultry and fish whereas non-heme iron is mostly present in plant-based foods such as legumes, fortified grains, dark chocolate, nuts, seeds and dark leafy vegetables.[117] About 10%–15% of total dietary iron intake comes from heme iron; however, due to its higher bioavailability, it can contribute to up to 40% of total iron absorbed. Moreover, enhancers and inhibitors of iron absorption also affect the bioavailability of iron. Heme iron and ascorbic acid increase absorption of iron from non-heme sources, while phytates (grains and legumes), polyphenols (tea and coffee), calcium (dairy products and supplements) and animal protein (milk protein, egg protein and albumin) inhibit its absorption.[118]

Therefore, a dietary strategy to improve iron status may include the consumption of a combination of heme iron-containing foods and non-heme iron sources coupled with foods high in ascorbic acid, which enhances non-heme iron absorption.[116] Foods high in iron absorption inhibitors should be consumed separately from an iron-containing meal. One study in adult women demonstrated that a 1 h time interval between an iron-containing meal and tea consumption attenuated the inhibitory effect of the tea.[119] Commonly, a 1–2 h interval between iron-containing meal and iron inhibitors is considered sufficient to minimise the negative impact of iron inhibitors on iron absorption.

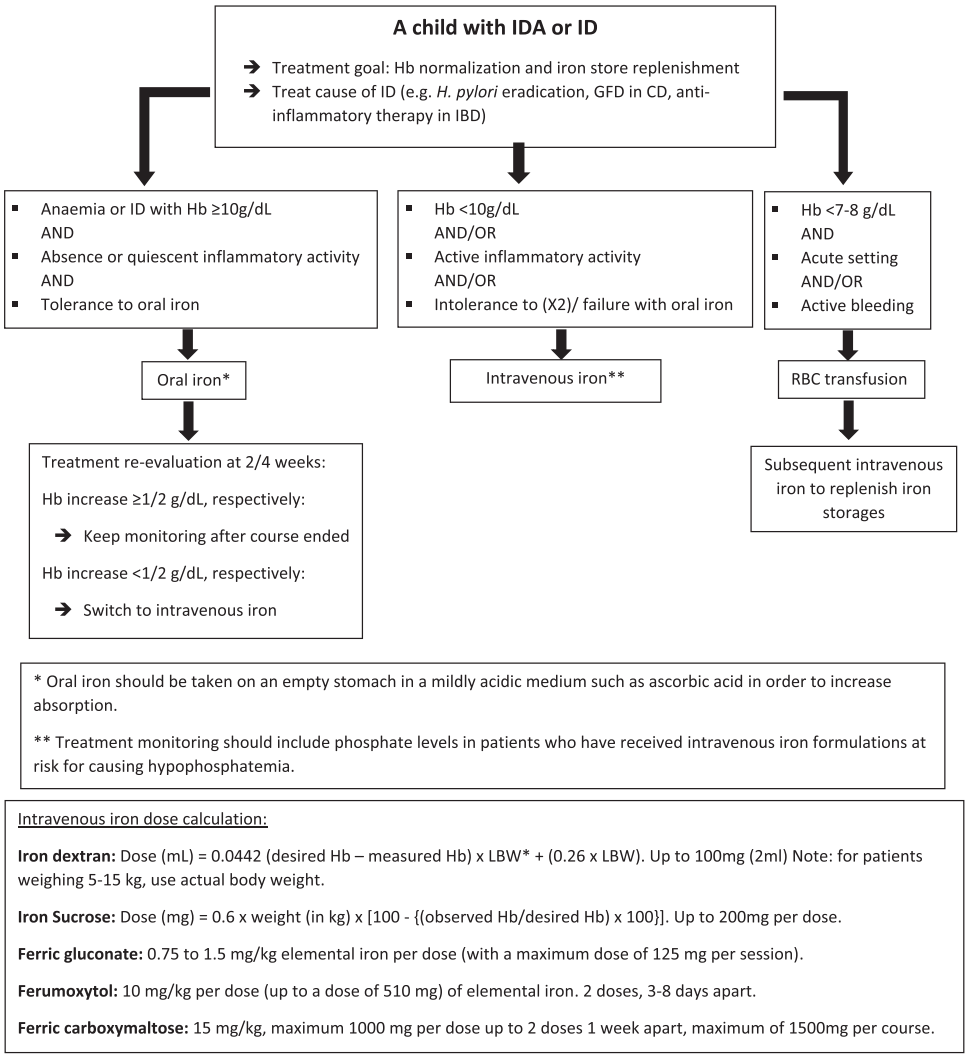

FIGURE 2 Therapeutic algorithm for children with IDA or ID. CD, celiac disease; GFD, gluten-free diet; Hb, haemoglobin; *H. pylori*, *Helicobacter pylori*; IBD, inflammatory bowel disease; ID, iron deficiency; IDA, iron deficiency anaemia; LBW, lean body weight; RBC, red blood cell.

Importantly, iron absorption is inversely correlated with iron status. Generally, absorption of heme iron is unaffected by an individuals' iron status, while absorption of non-heme iron is higher in individuals with decreased body iron stores.[119]

Recommended daily intake of iron ranges from 7 to 13 mg daily (adapted from EFSA Panel on Nutrition, Novel Foods and Food Allergens [120]) (Table 5). Many factors influence iron requirements, including age, sex and iron status, among others. Children who follow vegetarian or vegan diets require a higher iron intake since non-heme iron is less bioavailable than heme iron. Cow's milk is low in iron (0.1–0.2 mg per 240 mL) and is, therefore, not suitable for infants. In infants who are not breastfed, the only adequate source of iron is iron-fortified infant formula. By 6 months of age, the infant's endogenous iron stores will have been used up. Therefore, early introduction of foods rich in iron is recommended during complementary feeding period.[121] Table 6 lists the iron content of selected foods (adapted from Iron Fact Sheet for Health Professionals[122]).

6.2.2 | Oral iron

Oral iron preparations are relatively inexpensive and easily available but may cause GI side effects such as constipation, diarrhoea, abdominal pain and nausea while also having an effect on the intestinal microbiome.[115]

There are numerous iron preparations, most of them available as over-the-counter supplements with or without other vitamins or minerals, which may result in uncertainty for both patients and physicians. Ferrous sulphate is, currently, the most frequently used formulation, whereas ferrous gluconate, ferrous fumarate, and carbonyl iron have also demonstrated efficacy as iron supplements for prevention and treatment of IDA.[123–125] The elemental iron content of ferrous sulphate, ferrous gluconate, and ferrous fumarate is 20%, 11.6% and 33%, respectively. Iron polysaccharide combinations are hydrated microspheres remaining in solution over a wide range of pH values, theoretically allowing for improved absorption and tolerability.[115]

Recommended dosing in children ranges from 2 to 6 mg/kg/day, administered once a day, not exceeding the adult recommended dose of 100 mg of elemental iron per day.[126] A randomised controlled trial performed in rural Ghana compared ferrous sulphate preparation either as a single dose or as three divided daily doses and demonstrated similar results.[127]

A double-blind randomised trial in 80 children comparing ferrous sulphate with iron polysaccharide complex at a single daily dose of 3 mg/kg/day of elemental iron for 12 weeks found that ferrous sulphate was significantly more effective in the treatment of anaemia with an overall similar combined adverse events profile.[128]

In a study of adolescents and adults with IBD and mild anaemia, high CRP was associated with poor response, whereas lower baseline Hb was associated with better results following oral iron therapy.[129]

In a retrospective cohort study of 100 patients (≤21 years of age) with active ulcerative colitis and anaemia, 32 were prescribed standard oral iron supplementation therapy and demonstrated an increase in Hb of approximately 2.0 g/dL (95% confidence interval [CI]: 1.5–2.5) versus 0.2 g/dL (95% CI: 0.1–0.6) in non-treated patients ($p < 0.001$) by the time of their outpatient follow-up visit (median of 28 days).[130] In a recent retrospective cohort of children with IBD ($n = 76$) who were treated with oral sucrosomial iron (± in combination with intravenous ferric carboxymaltose in cases with moderate-severe anaemia), 61 patients (61 out of 76; 80%) had a significant increase in Hb levels (but not in ferritin) from 10.5 ± 0.4 to 11.6 ± 0.6 g/dL at 3 months and to 12.4 ± 1.2 g/dL at 9 months.[131] Nevertheless, at 3 months, only 37 patients (37 out of 76; 49%) had their anaemia corrected.[131]

In a randomised controlled trial enroling 200 *H. pylori*-infected children (2–5 years of age) with IDA or ID, it was shown that oral iron treatment for 90 days (with or without eradication) was significantly more effective than eradication alone for iron status replenishment.[132] Nevertheless, *H. pylori* eradication should be considered in cases of refractory anaemia. Meta-analyses of seven adult-based RCTs showed increased ferritin, following *H. pylori* eradication therapy plus iron therapy as compared with iron therapy alone.[133] In a recent paediatric case series of seven cases presenting with *H. pylori* associated refractory anaemia, eradication with subsequent 1–4 months of oral iron therapy resulted in a significant improvement of Hb, and ferritin.[134]

In a prospective study of 18 children with stable IBD, vitamin D supplementation without any other change of treatment (4000 international units daily for 2 weeks) resulted in a significant hepcidin reduction compared with baseline hepcidin that suggests vitamin D could play a role in the treatment of inflammation-

TABLE 5 Summary of dietary reference values for iron.

Age	Average requirement (mg/day)	Population reference intake (mg/day)
7–11 months	8	11
1–6 years	5	7
7–11 years	8	11
12–17 years (male)	8	11
12–17 years (female)	7	13

Note: Adapted according to EFSA Panel on Nutrition, Novel Foods and Food Allergens et al.[120]

TABLE 6 Iron content of selected foods.

Food	Iron content (mg) per serving
Grains and cereals	
Breakfast cereals, fortified with 100% of the daily value for iron, 30–40 g	18
Rice, white, long grain, enriched, parboiled, drained, ½ cup	1.4
Bread, whole wheat, 1 slice	0.8
Bread, white, 1 slice	1.1
Spaghetti, whole wheat, cooked, 1 cup	2.5
Animal-based sources	
Beef, rump steak, 100 g	3.6
Lamb leg, roasted, 100 g	1.8
Chicken, roasted, meat and skin, 100 g	1.3
Beef liver, 100 g	4.9
Egg, fried, 60 g	1.3
Salmon, steamed, 100 g	0.4
Cod, baked	0.1
Prawns, boiled	1.1
Legumes, nuts and seeds	
Lentils, boiled and drained, ½ cup	3.3
Kidney beans, canned, ½ cup	2.0
Cashew nuts, oil roasted, 18 nuts (30 g)	1.7
Green peas, boiled, ½ cup	1.3
Sesame seeds, whole, roasted and toasted, 30 g	4.2
Peanut butter, 1 tablespoon (16 g)	0.3
Vegetables and fruits	
Spinach, boiled and drained, ½ cup	3.2
Broccoli, boiled and drained, ½ cup	0.5
Tofu, firm, 100 g	2.7
Apricot, dried, 100 g	2.7
Fig, dried, 100 g	2.0
Milk and milk products	
Cow milk, plain, whole, 1 cup	0.0
Yoghurt, plain, 1 cup	0.1
Cheese, cottage, 2% milk fat, ½ cup	0.0

Note: Adapted according to Iron Fact Sheet for Health Professionals.[122]

related anaemia. However, the results of this study should be interpreted with caution due to the lack of a control group and the small number of patients included.[135]

Iron is recommended to be taken on an empty stomach at least 1–2 h before or after meals to minimise blockage of duodenal absorption while avoiding dairy products adjacent to iron intake, which may interfere with absorption. Ascorbic acid supplementation may improve absorption while PPIs can impair iron absorption.[115]

Duration of oral iron therapy is variable and should be guided by the severity of anaemia at treatment initiation and patient's response, but it usually lasts between 8 and 12 weeks. The response to iron therapy should be assessed after 2–4 weeks of treatment aiming for at least 1 g/dL increase in 2 weeks, or 2 g/dL in 4 weeks.[99] Before treatment termination, serum Hb and ferritin should be measured to confirm complete resolution of ID.

6.2.3 | Parenteral iron

Parenteral iron preparations are iron-carbohydrate complexes consisting of colloids or spherical iron-carbohydrate nanoparticles. The role of the carbohydrate shell, which varies in structure between preparations, is to stabilise the core and prevent or slow the release of bioactive free iron into the blood stream. These complexes are taken up by macrophages and following further degradation, release iron into the intracellular compartment. This iron is then exported via ferroportin and bound to transferrin for further transport. The unused iron is stored as ferritin.[136] The carbohydrate shell structure determines the stability of the complex. Formulations such as iron sucrose and ferric gluconate are less stable resulting in release of iron into the plasma. Iron binds to transferrin but when transferrin is saturated, the non-transferrin bound iron can provoke oxidative stress and in turn, Type 1 hypersensitivity reaction. Hence, these agents should be infused slowly and administered at a lower dose per infusion compared with the newer and more stable preparations such as ferric carboxymaltose and ferumoxytol. Intravenous iron may preferably be administered when disease is in remission in IBD, due to potential adverse effects of iron excess, which may occur when iron is administrated during active inflammation.[137] Nevertheless, there are no data to support this concern in children.

Numerous adult studies comparing different iron products have shown superior efficacy and tolerability of parenteral compared with oral iron products. A meta-analysis of mainly adults and older teenagers with IBD ($n = 1143$) has demonstrated an overall superiority of parenteral iron compared with oral iron therapy with response rates of 401 out of 505 patients (79%), 344 out of 508 patients (68%) and 147 out of 2019 patients (42%) with ferric carboxymaltose, iron sucrose and low-molecular-weight iron dextran, respectively.[138] Adverse

events were generally mild and did not differ significantly between formulations. Adverse events were reported (out of a pooled data of 1746 patients) in 65 out of 543 patients (12%), 72 out of 471 patients (15.3%) and 10/83 patients (12%) receiving ferric carboxymaltose, iron sucrose and low molecular weight iron dextran, respectively. Anaphylactic reactions were more common in low-molecular-weight iron dextran-treated patients. Evstatiev et al. demonstrated the superiority of ferric carboxymaltose over iron sucrose in adults with IBD, with response rates of 150 out of 240 patients (65.8%) versus 118 out of 235 patients (53.6%), respectively.[139]

A Cochrane meta-analysis which included 11 studies in adults with IBD concluded that intravenous iron administration, compared with oral treatment, may lead to more responders (relative risk [RR]: 1.17, 95% confidence interval (CI): 1.05–1.31, numbers needed to treat = 11), whilst withdrawals due to adverse events may be greater in oral iron-treated patients (RR: 0.39, 95% CI: 0.20–0.74).[140]

Although most studies include only adults, there is sufficient evidence, especially in the setting of IBD, that intravenous iron may also be safely administered to children with IDA. Adverse effects were associated more often with the administration of low-molecular-weight iron dextran (10 out of 119 [9%]) than with other formulations (9 out of 31 [29%]).[141,142] In children treated with iron sucrose, mean (±SD) Hb increased from 9.6 ± 1.2 g/dL at baseline to 12.1 ± 1.3 g/dL after iron sucrose treatment; adverse events were reported in 18 out of 273 (6.6%) infusions.[143] In another study including 142 children, hypersensitivity to iron sucrose was extremely rare.[144]

Ferric carboxymaltose has been administered more frequently in recent years. In a retrospective study including 72 children (0–18 years), mean Hb levels improved from 9.5 g/dL at baseline to 11.9 g/dL within 5–12 weeks.[145] An improvement in iron status in 51 children with ID (1–13 years) following one ferric carboxymaltose infusion was reported as (median, range) Hb: 2.7 (–2.4 to 7) g/dL, serum iron: 6.6 (–0.6 to 21.1 μmol/L) and transferrin saturation: 14 (–14% to 38%).[146] In another retrospective study including 72 children (11 months to 18 years) receiving ferric carboxymaltose, Hb normalised in 49 children (49 out of 72; 68%) and partial response was obtained in 22 patients (22 out of 72; 30%) with no serious adverse events, and only minor adverse events in 12 patients (12 out of 72; 16%) (mainly minimal urticaria).[147] In an uncontrolled prospective trial using ferric carboxymaltose in children with IBD, resolution of ID was noted in 28 out of 44 (64%) and in 66 out of 57 (81%) children with IDA or ID, respectively.[148] In a more recent trial, 128 children with IBD (3–18 years) were treated with ferric carboxymaltose. Most children (81 out of 128; 63.3%) required only one infusion. Mean Hb improved (regardless of disease activity) from 10.7 ± 1.5 to 12.4 ± 1.2 g/dL while median ferritin increased from 14.0 (5.5–34.5) to 163.7 (91.0–285.0) 4–6 weeks following treatment.[149] Twenty-five children (25 out of 128; 19.5%) had low post-infusion serum phosphate, whereas two children experienced severe hypophosphatemia. In a very recent Phase 2 trial, children with a baseline Hb of <11 g/dL (ages 1–17 years) were allocated to either 7.5 mg/kg ($n = 16$) or 15 mg/kg (n = 19) of ferric carboxymaltose. On Day 35 post-infusion, the mean change in Hb values was greater in the higher dose group (2.8 vs. 2 g/dL) with no significant difference in safety signal.[150]

Scarce data are available on the use of ferumoxytol in children. A retrospective report in 54 children (1 month to 19 years) with anaemia of diverse aetiologies found significant improvement in iron status in most patients with minor adverse events in 4.5% (2 out of 54) of the infusions and moderate-severe reactions in 2.7% (1 out of 54) of the infusions.[151]

The dose calculation of parenteral iron formulations in children differs among each preparation but the final treatment goal should be not only to normalise Hb concentration but also to replenish iron stores.

6.2.4 | Indications for blood transfusion

There are no solid guidelines for blood transfusion in children with GI conditions and anaemia. The decision to transfuse should be based on the stability of the patient, ongoing blood loss, and how quickly the anaemia has developed. A threshold of 7–8 g/dl was suggested in children with IBD.[99] Nevertheless, in a recent comprehensive meta-analysis of 45 studies (including three paediatric studies), comparing the restrictive RBC transfusion strategy (<7–8 g/dL) to liberal transfusion strategy (<9–10 g/dL), the restrictive strategy did not impact 30-day mortality, mortality at other time points, or morbidity (i.e., cardiac events, myocardial infarction, stroke, pneumonia, thromboembolism and infection), compared with a liberal transfusion strategy, but decreased the proportion of people exposed to RBC transfusion by 41%.[152]

7 | RESULTS AND CONCLUSIONS

Anaemia remains a diagnostic challenge in children with GI disease as there are various causes leading to a decrease in Hb levels. Initial therapy may not always directly lead to success. This position paper tries to facilitate a correct diagnostic approach considering a broad differential diagnosis to establish efficacious therapeutic options weighing advantages and disadvantages as well as pitfalls along the most recent literature. In view of the importance of anaemia in clinical routine, thorough diagnostic and therapeutic algorithms will give clinicians valuable assistance in treating children with GI disease and anaemia. Recommendations and practice advice are based on

available paediatric evidence with inference from adult-based studies and literature when necessary, but where evidence is still lacking, recommendations rely on expert opinion.

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