Belgian Recommendations for the management of anemia in patients with inflammatory bowel disease

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Abstract

Anemia is the most common extraintestinal manifestation of inflammatory bowel disease (IBD) which, in most cases, results from an absolute or functional iron deficiency. Although anemia and iron deficiency may have a dramatic impact on the quality of life of IBD patients, they are underdiagnosed and undertreated. This paper provides evidence-based consensus guidelines and practical treatment algorithms that are directly applicable to the Belgian situation. In this way, the Belgian IBD research and development Group (BIRD) aims to increase awareness and knowledge among gastroenterologists in order to improve the management of anemia and iron deficiency in their IBD patients. (Acta gastroenterol. belg., **2014**, 77, **333-344**).

Key words : inflammatory bowel disease, anemia, iron deficiency, guidelines.

I : Prevalence of anemia in IBD

Statement I-a

Anemia is the most common extra intestinal manifestation of IBD, but remains underdiagnosed and undertreated (EL3).

Statement I-b

Anemia is most prevalent in young patients, Crohn's disease, admitted patients and in the early stage of the disease (EL3).

Statement I-c

Iron deficiency is more prevalent than anemia in IBD (EL 3).

Global prevalence

Crohn's disease (CD) and ulcerative colitis (UC) are idiopathic inflammatory bowel diseases (IBD). The cardinal presenting symptoms are abdominal pain, diarrhea and weight loss. Apart from the typical intestinal symptoms, extra-intestinal manifestations, including skin lesions, arthropathy, uveitis and primary sclerosing cholangitis are frequently seen (1,2). Also anemia is a common complication of IBD. The prevalence is reported to encompass a wide range. Since some authors reported a prevalence up to 74% (3), the question raises whether anemia is a side effect of IBD or rather a cardinal symptom. Due to the wide reported range it is best to evaluate the prevalence of anemia in IBD in the light of the different settings : age, type of diagnosis, care setting and time after diagnosis (Fig. 1).

Prevalence according to age

Prevalence varies according to the age of patients with a trend for a higher prevalence in younger patients. This difference is partially explained by the different disease phenotype of IBD in children and adolescents (4). A cross-sectional study demonstrated that anemia in general is significantly more prevalent in children (70%) compared to adolescents (42%) and adults (40%). Predominantly iron deficient anemia (IDA) is more often present (5,6). These data were confirmed in other pediatric cohorts with prevalences reaching 70-72% at diagnosis, mostly in young girls (5,7). Moreover, anemia is more frequently undertreated in children than in adults (6). In the year following diagnosis only 28% of the anemic children received any form of iron therapy (8).

Prevalence according to diagnosis

Although CD and UC have a similar pathogenesis, the different distribution of the disease can also affect the prevalence of anemia. Globally, anemia is more common in CD compared to UC (9,10,11,12,13). Disturbed proximal absorption by involvement of the proximal gastrointestinal tract and extensive intestinal resections together with a more severe disease activity in CD are possible explanations for the difference in prevalence of anemia (14).

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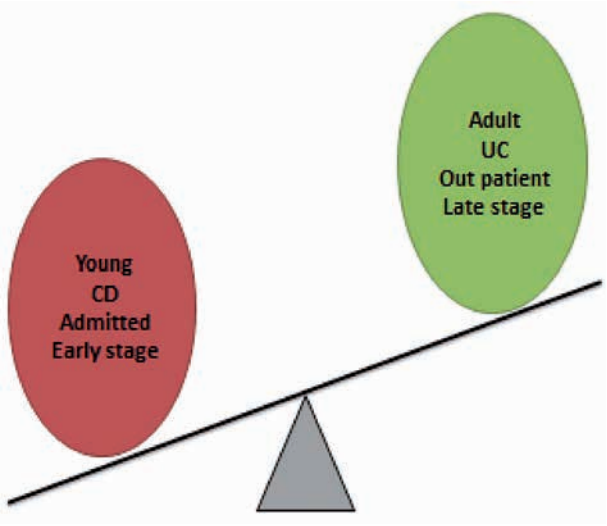

Fig. 1. — Relative imbalance in prevalence of anemia in IBD according to setting. Red oval : anemia more prevalent, green oval : anemia less prevalent.

Prevalence according to setting

Older studies in general report a very high prevalence of anemia in hospitalized patients mostly affected by a more severe disease (3). A Swiss study compared patients in referral centers to patients in private practices and confirmed the significant higher prevalence of anemia in referral centers reflected by a higher disease activity (15). Patients hospitalized in the past year have a higher chance of having anemia (9).

Prevalence according to time from diagnosis

One of the major factors that have an impact on anemia in IBD is the adequate treatment of the underlying disease. A pediatric cohort showed a decrease of 32% in anemia one year after diagnosis and even a more dramatic fall in severely anemic patients (7). However, three months after initiation of treatment 47% of patients remained anemic (16). In another pediatric cohort, 30% remained anemic after 2 years of follow-up (5). A Scandinavian 10-year follow-up study showed a progressive decline in anemia rates over time after diagnosis except in women with CD where the anemia rates stabilized from 1 year after diagnosis onwards (13). The type of anemia also differs depending on the time after diagnosis. In the early stage of the disease most patients have an anemia of chronic disease, whereas more patients in follow-up have the iron deficient type of anemia (12,14).

Prevalence of iron deficiency

Not only prevalence of anemia varies, true iron deficiency (ID) is reported in 36% and 90% of patients. The differences between trials are mainly based on the cohort studied and the definition of ID (3,11). In general , iron deficiency is more common than anemia (11). There is discussion on the relevance of ID in the absence of anemia. Treatment of ID in absence of IDA resulted in longer time to anemia recurrence, but had no impact on the quality of life of patients (17).

II : Causes of anemia in IBD

Statement II-a

Iron deficiency anemia and anemia of chronic disease are the 2 principal causes of anemia in IBD, and combination of both is frequent (EL3).

Although iron deficiency is very common in IBD, iron deficiency is not synonymous for anemia. Anemia in IBD has multiples causes. As stated before the cause of anemia can also change over time (12). The two most common causes of anemia in IBD are IDA and ACD. Those two main forms have a strong interaction. Active inflammatory bowel disease is marked by inappropriate intake, blood loss from mucosal ulcerations, altered absorption after intestinal resection and interaction with erythropoiesis by cytokine production. This means that in active disease, a combined etiology of anemia is mostly present (18) (Fig. 2).

Iron deficiency anemia

The causes of IDA are not well studied but are based on an imbalance between intake and absorption at one side and blood loss at the other side. Since iron is absorbed in the duodenum and proximal jejunum probably only patients with proximal CD will have inadequate absolute iron uptake, this needs to be distinguished from a functional iron malabsorption (see below). Studies on this topic are very conflicting and varies between no alterations in iron absorption to 90% reduction (3). There are no quantitative studies focusing on intestinal blood loss and ID.

Anemia of chronic disease

In active IBD the inflammation itself is a possible cause of anemia. The pathogenesis of ACD follows different pathways. Firstly, Hepcidin is an acute phase protein that plays a pivotal role in the regulation of iron absorption (19). The expression of hepcidin gene is upregulated during inflammation and mainly triggered by interleukin 6 (20). Hepcidin blocks ferroportin in the cell membrane of enterocytes and macrophages. By this action iron is stored intracellularly and is not available for erythropoiesis resulting in a functional iron deficiency or malabsorption (21). This effect is aggravated in acute inflammation by the shorter life span of erythrocytes and erythrophagocytosis by macrophages leading to retention of iron in the macrophages (22). Secondly pro-inflammatory cytokines have a negative impact on the production and biological activity of erythropoietin (22,23). A higher amount of erythropoietin is needed to stimulate the erythroid progenitor cells by an interac-

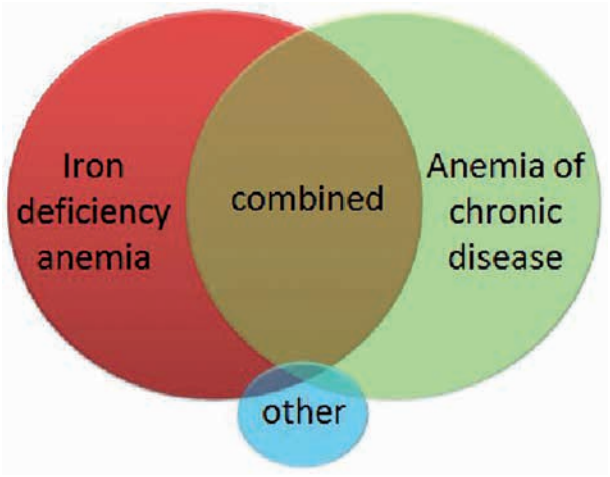

Fig. 2. — Causes of anemia in IBD

tion with the erythropoietin receptors and blunting of the downstream intracellular pathways (21,22). Finally, inflammation also interferes with the formation of erythroid colony-forming-units and blood-forming-units in the bone marrow. This inhibits the differentiation and proliferation of progenitor cells (22,24).

Other causes of anemia

Apart from the above described main causes, anemia in IBD can also be induced by vitamin deficiencies, such as vitamin B12 and folic acid, mainly in patients with ileal resections and extensive small bowel disease (18). In general folic acid deficiency is more common than vitamin B12 deficiency (3). Some treatments can induce anemia. Sulfasalazine affects erythropoiesis by several mechanisms including folate absorption, hemolysis and aplasia (3,25). Myelotoxicity is a severe and possible lethal side effect of thiopurine analogs, although isolated anemia is rare (26). The degree of myelosuppresion is linked with the level of thiopurine-methyl-transferase. Other types of anemia have been reported in IBD, such as hemolytic anemia, myelodysplastic syndromes and hemoglobinopathies without direct causality (3).

III : Diagnostic strategies for anemia in IBD

Statement III-a

The WHO definitions of anemia apply to patients with IBD. All IBD patients must be assessed for the presence of anemia (EL3).

Statement III-b

Minimal laboratory screening tests at baseline workout must include hemoglobin, ferritin, serum iron+transferrin saturation, CRP, vitamin B12, folic acid, haptogloblin, lactate dehydrogenase and serum creatinine (EL3).

Statement III-c

Measurements are best performed at least every 3 months for patients with active disease and every 12 months for patients in remission (EL3).

Statement III-d

Combination of transferrin saturation (TfS) and ferritin permit to differentiate ACD from IDA in most cases (EL3).

Statement III-e

New alternative markers as reticulocyte hemoglobin content CHr, soluble transferrin receptors (sTfR) :log ferritin ratio and hepcidin could be considered to affine the differential diagnosis (EL3).

Statement III-f

Others causes of anemia must be excluded (EL3).

Anemia is defined by the World Health Organization (WHO) as a hemoglobin (Hb) concentration < 12 g/dL in non-pregnant women and < 13 g/dL in men (27).

Initial laboratory screening of anemia in IBD includes markers permitting : 1) to assess the anemia and iron deficiency such as Hb, complete blood count including reticulocytes, serum iron, ferritin and transferrin saturation (TfS) ; 2) to detect the level of disease activity in IBD such as C-reactive protein (CRP) and fecal calprotectin and 3) to exclude others causes of anemia such as vitamin B12, folic acid, haptogloblin, lactate dehydrogenase, Hb electophoresis and serum creatinine.

IBD patients in clinical remission should be screened at least every 12 months, whereas patients with active disease at least every 3 months or at shorter intervals depending upon their iron status (28).

Iron deficiency anemia or/and anemia of chronic disease

Iron deficiency anemia and anemia of chronic disease are the two most common causes of anemia in IBD and represent often overlapping conditions, making the differential diagnosis between them difficult. The combination of the TfS and serum ferritin levels are proposed to define IDA, ACD or a mixed situation of both : 1) In the absence of any sign of inflammation, the diagnosis of IDA can be made when IBD patients present a low Hb (men < 13 g/dL and women < 12 g/dL), a transferrin saturation less than 20% and a ferritin concentration below 30 ng/ml. ; 2) In the presence of active IBD, the diagnosis of ACD can be made when IBD patients have a low Hb (men < 13 g/dL and women < 12 g/dL), low TfS (< 20%) and ferritin concentrations above 100 ng/ml ; 3) a combination of IDA and ACD should be considered when IBD patients present an active IBD with low Hb (men < 13 g/

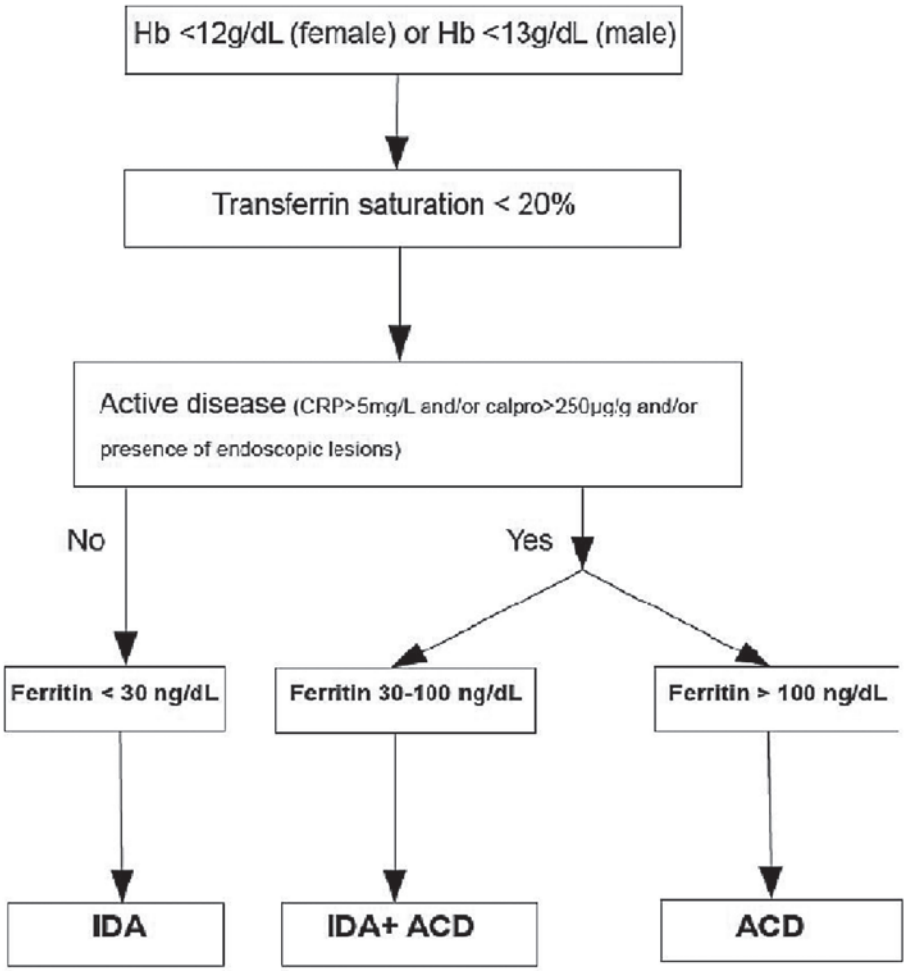

Fig. 3. — Diagnostic algorithm for anemia in IBD using conventional markers

dL and women < 12 g/dL), low TfS (< 20%) and a ferritin concentration between 30 and 100 ng/ml (Fig. 3).

Combination of TfS and serum ferritin

TfS is a measurement of the iron content of the circulating transferrin (TRF). TfS gives an indirect indication of the extent of iron use in the bone marrow but does not provide any information about the iron stores, indirectly estimated by ferritin, the iron store protein. In the guidelines for diagnosis of anemia in IBD, a cut-off TfS value of < 20% is proposed in combination with serum ferritin to detect IDA (28-29). Serum ferritin is an acute-phase reactant and its concentration may be increased in some conditions like fever, acute infections, malignancies or chronic inflammatory disorders including IBD. In inflammation, the storage iron is not released to circulating transferrin, resulting in a high serum ferritin and low TfS level. A cut-off ferritin level of < 30 ng/ml has a sensitivity of 92% and specificity of 98% for IDA while a ferritin level of > 100 ng/ml mostly excludes IDA (30).

Additional conventional markers for iron status

Erythrocyte markers as red cell distribution width (RDW), Mean corpuscular volume (MCV), Mean corpuscular Hb (MCH) are also proposed as conventional diagnosis markers of anemia in IBD. The wide range of RDW and MCV values has diminished its usefulness in differential diagnosis between IDA and ACD. A low MCH (< 27 pg) rather than low MCV (< 80 fL) became the most important red cell markers for detecting IDA, but there might be an impact of treatments used in IBD or vitamin deficiency (31).

New alternative markers for iron status

Beside the conventional markers, new generation parameters seem to be very promising in order to better differentiate between IDA and ACD in IBD patients : iron status markers as soluble transferrin receptors (sTfR) and sTfR :log ferritin ratio (ferritin index) ; reticulocyte markers as reticulocyte hemoglobin content (CHr) and iron metabolism markers as hepcidin and prohepcidin. Serum iron is delivered to cells via transferrin receptor (TfR1). A truncated soluble form of the TfR1 (sTfR1) circulates in the plasma and its concentration reflects the cellular requirement for iron. sTfR1 and its ferritin index are very useful in the differential diagnosis between IDA and ACD in IBD patients knowing that sTfR1

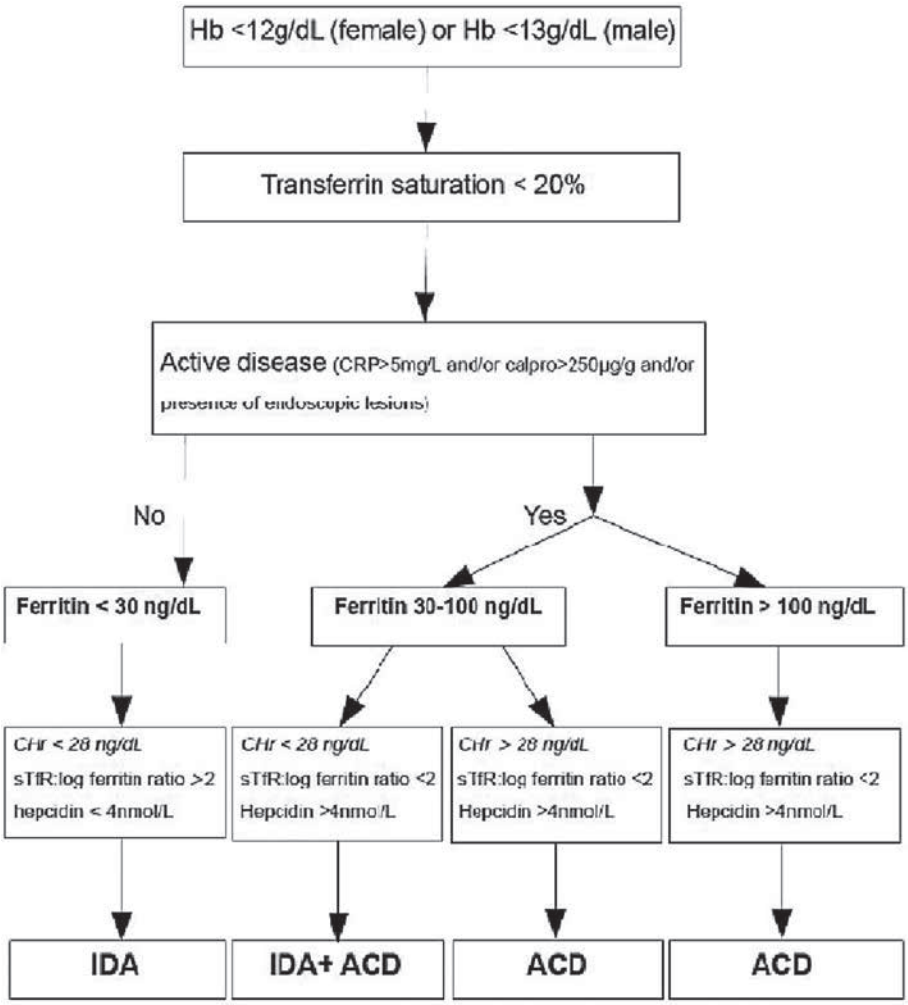

Fig. 4. — Diagnostic algorithm for anemia in IBD using conventional and new markers

concentration, unlike serum ferritin and TRF, is not influenced by chronic inflammation. A cut-off value of sTfR :log ferritin ratio < 2 is proposed in the confirmation of ACD (31-35). CHr is an indirect measure of functional iron available for new red blood cell production over the previous 3-4 days. CHr provides also an early measure of the response to iron therapy, increasing within 2-4 days after the initiation of the iron therapy. A value of CHr < 28 pg was found to predict IDA more accurately than serum ferritin or TfS. A CHr < 28 pg combined with sTfR :log ferritin ratio < 2 can also be used to differentiate combined ACD and IDA from ACD (normal CHr). CHr could also be useful to measure early response to intravenous iron therapy (34,36). Hepcidin is a circulating peptide which is a key regulator of the systemic iron homeostasis and is produced trough prohepcidin, a precursor protein. Hepcidin expression is negatively or positively controlled by respectively iron or inflammation. Hepcidin levels are significantly higher in IBD patients compared to healthy controls. Significant correlations of hepcidin with ferritin, CRP and disease activity of IBD are also found. A hepcidin cut-off level > 4 nmol/L is proposed to confirm ACD and to differentiate it from IDA. Differential diagnosis between combined ACD and IDA and ACD is given by the hepcidin plot as a hepcidin > 4 nmol/L with a CHr < 28 pg (37) (Fig. 4).

Disease activity of IBD

Clinical, biological and endoscopic evaluation of disease activity of IBD is useful in the differential diagnosis between IDA and ACD and in the treatment strategies. In active disease with IDA, an optimization of IBD treatment is recommended in parallel of IV iron supplementation. Biological evaluation of disease activity includes a dosage of serum CRP (> 5 mg/L) and/or of fecal calprotectin (> 250 µg/g). Endoscopic investigation is also recommended to evaluate the presence of GI mucosal ulcerations.

IV : Treatment of anemia in IBD

Statement IV-a

Iron substitution has to be given to all IBD patients with a hemoglobin level below normal and proven iron deficiency (EL4).

Statement IV-b

Regarding to the treatment of iron deficiency anemia in IBD, intravenous iron is more effective and better tolerated than peroral iron (EL1).

Statement IV-c

For IBD patients with severe anemia (Hb less than 10.5 g/dl) and active disease, the intravenous route of iron supplementation has to be chosen (EL1).

Statement IV-d

In case of insufficient control of anemia despite intravenous iron and optimalisation of IBD therapy, an erythropoeitin stimulating agent in combination with intravenous iron has to be considered (EL2).

Rationale for the treatment of anemia in IBD

There is sufficient evidence in literature demonstrating that quality of life in IBD patients improves with the correction of anaemia and that this improvement is independent of the disease activity (38).

While it is known that iron deficiency may induce a variety of symptoms even in the absence of anemia (eg. fatigue, reduced exercise tolerance, headache, nail growth defects, libido loss, erectile dysfunction...), the benefit of iron supplementation in non-anemic IBD patients with defective iron stores is controversial (39). Many reports have shown that iron-replacement therapy in non-anemic patients with defective iron stores can improve fatigue, exercise performance, muscle function and quality of life in patients with chronic fatigue or heart failure, but such evidence is not yet available in the context of IBD (39,40). The decision to supplement iron in IBD patients without anaemia should therefore be made on an individual basis (history of the patients, individual preference), but with caution for oversubstitution.

Aim of the treatment of anemia in IBD

The final goal of the treatment of anemia in IBD is the improvement of the patient's quality of life. To monitor an optimal treatment of anemia in IBD, the following measurable targets can be used (28) :

1.a) a gain of 2 g/dL Hb within four weeks, OR
1.b) the achievement of a normal Hb level within four weeks
AND
2) a transferrin saturation > 30%.
AND
3) a ferritin concentration between 200 and 300 µg/L

Transferrin saturation levels > 50% and ferritin levels > 800g/L should be avoided, as these levels are within a toxic range (28).

Non-ferriprive anemia

In anemic IBD patients without evidence of iron deficiency, other causes have to be excluded. Patients with active disease might have a "pure" anemia of chronic disease. In these patients, anemia will normally resolve upon correction of the underlying inflammation (41). A drug-induced cause of anemia always has to be kept in mind, especially when the patient is taking sulphasalazine, purine-analogues or methotrexate. For purine-analogues and methotrexate, anemia almost always occurs in the setting of a generalized myelodepression and can often be managed by dose reduction. The risk of myelodepression with purine-analogues can be partially predicted by thiopurine methyltransferase (TPMT) genotyping or assessing TPMT enzyme activity (42).

Ferriprive anemia

Calculation of the total body iron deficit

For many years, the Ganzoni formula (total body iron deficit in mg = (body weight in kg×[target hemoglobin — actual hemoglobin in g/dL]×0.24)+500) has been used to calculate the total iron deficit. This formula is inconvenient and prone to errors. In addition, it has become clear that the Ganzoni formula underestimates the iron requirements (43). A simple, fixed dosing regimen based on baseline haemoglobin and body weight is much more practical for the treating physicians and might also be more efficacious (Table 1).

Oral versus intravenous formulations ?

Several points should be considered when choosing the route of iron administration in IBD patients :

a) A big advantage of oral iron substitution is that it is very cheap and does not require hospitalization. The total cost for a complete iron supplementation of 1500 mg iron is between 10-60 euro for oral preparations (not reimbursed by social security) and about 200 euro for intravenous preparations (mostly reimbursed - only +/-10% paid by the patient) in Belgium.

b) Up to 90% of orally administered iron remains unabsorbed in the gut lumen, which results in gastrointestinal side effects in about 50% of the patients (nausea, abdominal bloating, altered bowel movements). These side effects often result in bad patient compliance and early cessation of the therapy (44).

c) In patients with active inflammatory bowel disease, iron-deficiency anemia and anemia of chronic disease often coincide. The inflammation-mediated induction of hepcidin, which regulates iron homeostasis, may result in suboptimal gastrointestinal absorption and hence, reduced responsiveness to orally administered iron (20). As such, patients with active IBD may benefit from intravenous iron.

d) Some concerns have been put forward on the potential effect of luminal iron on the activity of IBD. Studies in animal models of IBD have shown that the production of reactive oxygen species by intraluminal iron may

Table 1. — **Calculation of the total iron deficit based on bodyweight and hemoglobin level**

Bodyweight	< 70 kg		> 70 kg	
Hemoglobin level	≥ 10 g/dL	< 10 g/dL	≥ 10 g/dL	< 10 g/dL
Cumulative dose needed	1000 mg	1500 mg	1500 mg	2000 mg
Dosage week 1 (for IV route)	1000 mg	1000 mg	1000 mg	1000 mg
Dosage week 2 (for IV route)		500 mg	500 mg	1000 mg

1) modify the colonic microbiotia, 2) worsen intestinal inflammation and 3) have carcinogenic potential (39). Probably the strongest animal evidence comes from Werner *et al*., who showed that chronic terminal ileitis in TNFDARE mice, a murine model for Crohn's disease, could be completely prevented by an iron-depleted diet (45). Up till know, there is no convincing evidence for harmful effects of intraluminal iron in human IBD patients, except for a small study in African children, in whom dietary iron supplementation was shown to affect the colonic microbiota and increase faecal calprotectin-levels, a marker of gut inflammation (46).

e) Three recently published meta-analyses comparing oral versus intravenous iron supplementation for the treatment of Iron deficiency anemia in IBD showed superiority of intravenous iron therapy in terms of hemoglobin gain, ferritin gain and adherence to therapy (44,47,48). On the other side, a recently published multicenter randomized open-label trial failed to demonstrate non-inferiority of IV iron isomaltose compared to iron sulphate in terms of change in hemoglobin after 8 weeks of treatment, and thereby reinforces the concerns on the cost-effectiveness of a first-line parenteral iron substitution in IBD (49,50).

f) In Belgium, reimbursement criteria for intravenous iron therapy in IBD have been defined, that are limiting its use for IBD patients (Table 2). Note the presence of "documented iron malabsorption" as one of the criteria. No specification concerning the documentation of iron malabsorption is provided. As iron is absorbed in the small bowel, it is assumed that Crohn's disease patients with active small bowel disease or previous intestinal resections will have some degree of iron malabsorption. Hence, in these patients, a direct choice for intravenous formulation can be made. Noteworthy is the fact that intolerance for oral iron, which is often the reason for cessation of the therapy, is not a sufficient reimbursement criterium in Belgium.

Specific considerations for peroral iron replacement therapy

Iron is best absorbed as the ferrous (Fe^{++}) salt (ferrous fumarate, ferrous sulfate, ferrous gluconate) in a mildly acidic medium. For this reason, some companies have combined iron and ascorbic acid or folic acid in their tablets. Alternatively, if no acid is added to the formulation itself, the iron tablet can be administered with a glass of orange juice. Ferric (Fe+++) salt formulations are more expensive without a proven superiority with regard to efficacy or tolerability.

Gastrointestinal side effects are dose-dependent. Usually, a dose of 100mg of Fe^{++} is prescribed. Ideally, the intake should be before the meal. An intake during or after the meal reduces the gastrointestinal side effects, but also the absorption which results in a less effective treatment.

In case of good patient compliance and a normal response, the hemoglobin concentration will rise slowly, usually beginning after approximately one week of treatment. Over the ensuing three weeks, the hemoglobin concentration will normally increase with 2 g/dL (51).

A 6-month course of oral iron is usually needed to completely replenish iron stores (51).

Specific considerations for intravenous iron replacement therapy

Several new IV iron preparatations have entered the market. In contrast to older preparations, they are not associated with anaphylactic reactions. As such, no test dose is required and high doses at once can be given.

In Belgium, only iron dextran (fercayl®), iron sucrose (Venofer®) and iron carboxymaltose (Injectafer®) are licensed IV iron formulations. As dextrans carry a substantial risk of anaphylactic reactions and iron sucrose needs to be given in several doses of 200 mg, most centres have switched to the newer iron carboxymaltose (Injectafer®). Iron carboxymaltose can be given at doses of 1000 mg at once, is safe and well tolerated. Depending on the bodyweight and the hemoglobin level of the patient, a full iron supplementation can be provided in 1 or 2 doses.

The FERGIcor trial demonstrated superiority of ferric carboxymaltose (with fixed dose regimen based on bodyweight and baseline hemoglobin level) compared with iron sucrose (with dose regimen based on the Ganzoni formula) in terms of gain in hemoglobin, transferrin saturation and ferritin after 12 weeks of treatment (52). A specific and transient side effect of ferric carboxymaltose was an (asymptomatic) hypophosphatemia (52).

Preventing recurrence of iron deficiency anemia ?

In an extension study of the FERGIcor trial (FERGI-main), the recurrence rate of anemia in nonanemic patients that had completed the FERGIcor trials was about 40% after only 8 months of follow-up. A preventive IV dose of 500 mg ferric carboxymaltose if the ferritin level dropped below 100 μg/L (measured at 2-month intervals) could reduce the recurrence rate to 26,7% (17). Future studies will have to investigate whether such a pro-active ferritin-triggered anemia-prevention is cost-effective and improves the quality of life of IBD patients.

Table 2. — **Current reimbursement criteria for intravenous iron supplementation in IBD**

1) Hemoglobin < 10.5 g/dl Or one of the following: 2) Failure of oral iron after two months (goals not reached) 3) Proven and documented iron malabsorption 4) Intolerance for peroral iron and persisting anemia (2 times Hb < 8 g/dl with at least one month interval)

Erythropoeitin stimulating agents

There is evidence that IBD patients in whom intravenous iron failed to correct the anaemia

will respond to the addition of erythropoietin stimulating agents (39). It is important to know that these agents should always be combined with intravenous iron, to ensure adequate bone marrow iron reserves to enable an effective erythropoetic response (39). Erythropoietin stimulating agents are very expensive and also carry a substantial risk of vascular thrombosis, for which the risk is already increased in IBD patients (53). Their indication should therefore be strong and made on individual basis. The optimal dosing regimen for EPO in the context of IBD still has not yet been defined.

Red blood cell transfusion

Several lines of evidence suggest that, even in the case of an acute bleeding, a restrictive transfusion policy is at least as effective as, and safer than, a more liberal policy (54). The role of blood cell transfusion in patients with IBD should be restricted to life-threatening situations, where a very fast correction of the anemia is required. The cut-off hemoglobin value for transfusion has not been defined in clinical trials, but most guidelines suggest a value between 6 and 8 g/dl (32,54). However, even with these values, the anemia can be chronic and well tolerated. Hence, decision-making should be on an individual basis.

A correct management of anemia should lead to anecdotical need for blood transfusion in IBD patients.

Management of anemia in IBD patients in daily clinical practice in Belgium

After a diagnosis of anemia (Hb < 12 g/dl and Hb < 13 g/dl respectively for female and male patients), a screening for iron deficiency should be performed by measuring the transferrin saturation. The transferrin saturation can easily be calculated by using the following formula :

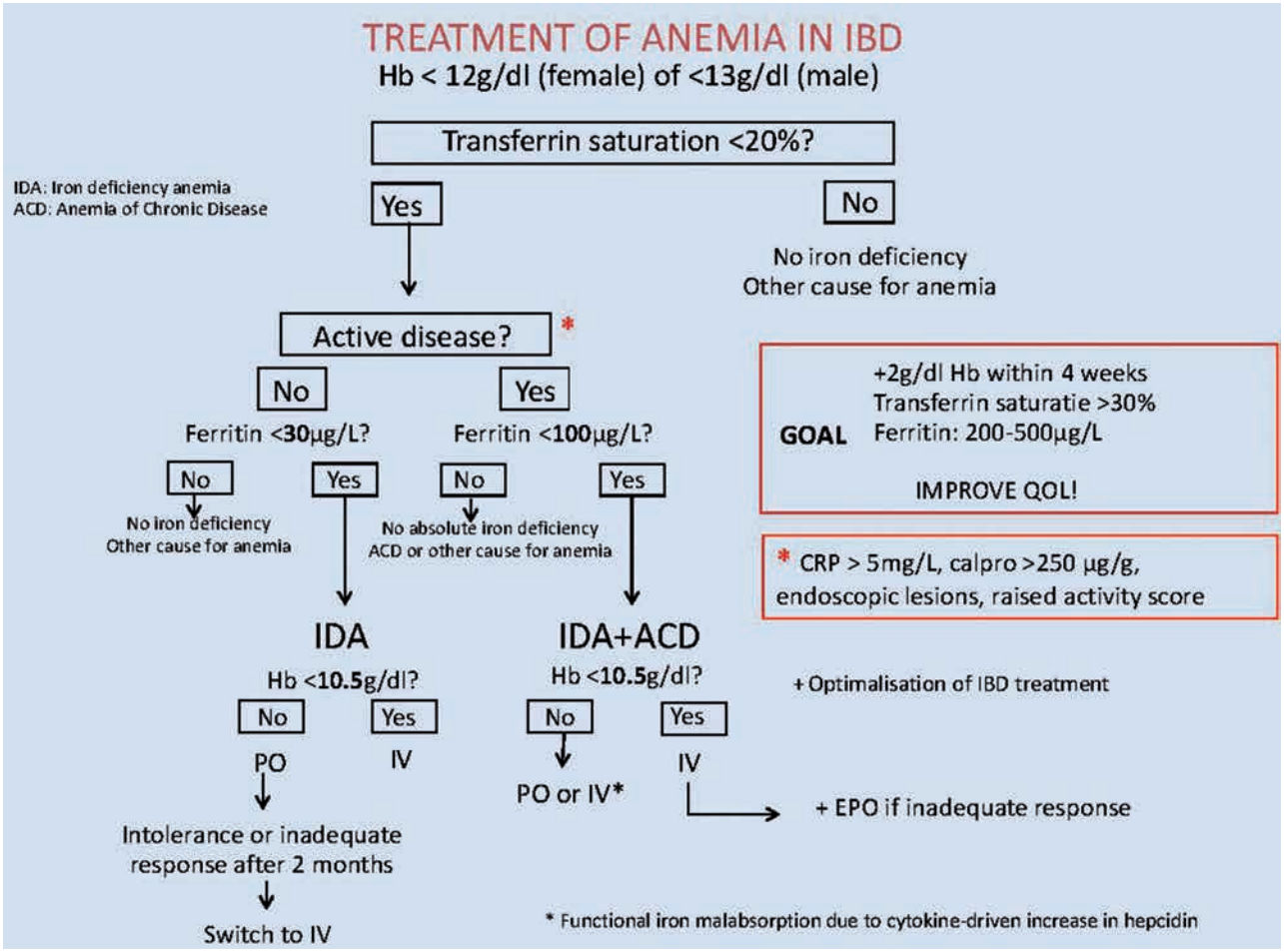

Fig. 5. — Therapeutic algorithm for the treatment of anemia in IBD

Transferrin saturation = serum iron ×100/total iron binding capacity (TIBC = transferrin ×1.25)

A transferrin saturation > 20% means that there is no iron deficiency and other causes of anemia should be looked for. If the transferrin saturation is below 20%, ferritin levels of 30 µg/L and 100 µg/L are the lower limits of normal for quiescent and active IBD respectively. Only in case ferritin levels are below these thresholds, a firm diagnosis of iron-deficiency can be made. If not, other causes for anemia should be looked for. The route of iron replacement is based on the hemoglobin level of the patient and the disease activity. In case the Hb is below 10.5 g/dL, the patient meets the reimbursement criteria for intravenous iron. In case the Hb is equal to or above 10.5 g/dl, the peroral route should be chosen unless the patient is suffering from active disease and hence, a functional iron malabsorption can be expected due to cytokine-driven increase of hepcidin levels. For these patients, a direct choice for intravenous iron can be made. In all other cases, intravenous iron can only be prescribed if the patient does not show the expected response after two months of treatment. In patients with active IBD, a treatment optimization and better control of the inflammatory process will often lead to an amelioration of the anemia as well. In patients that show an insufficiënt response to intravenous iron, concomittant administration of erythropoietin should be considered.

V : Specific considerations for anemia in pediatric IBD patients

Statement V-a :

Anemia in children is under treated (EL2)

Prevalence of anemia in pediatric IBD

Although anemia in IBD is more common in children than in adults, far less is known about the diagnostic criteria and the optimal treatment strategy. Literature on anemia in IBD children is limited to a few retrospective descriptive studies of the presence, evolution and current treatment practices (5,6,8). These studies reveal an undertreatment of anemia in pediatric IBD (6,8). The younger the patients, the lesser iron therapy is used. In a retrospective study from Goodhand, fewer iron deficient children (14%) than adolescents (30%) or adults (48%) are given oral iron and none have received IV iron compared with 30% adolescents and 41% adults (6) The same was concluded in the study from Gerasimidis (7). Plausible causes can be identified : the lack of studies that have demonstrated a positive effect of iron treatment, the concern of possible side effects of the medication, the concern about worsening the disease activity and the belief that children are more tolerant to anemia due to a lack of studies relating anemia to quality of life (6,8). Moreover, IV Iron is not registered for use in young children in many countries.

On the other hand, the prolonged prevalence of anemia can also be due to changes in disease activity and therefore undertreatment of the inflammation needs to be considered also (7).

Diagnosis of anemia in pediatric IBD

The cut-off hemoglobin levels for the diagnosis of anemia in children according to WHO criteria are : in children age 5-11 years < 11.5 g/dL, in children age 12-13 years < 12 g/dL, and above the age of 13 years, the same cut-offs as for adults are used.

To differentiate between IDA and ACD, several definitions are proposed in adults, but they are not applicable as such in children. Normal ferritin values increase according to age, therefore, WHO has formulated the following definitions :

	Serum ferritin (µg/L)	
	Less than 5 years of age	5 years of age or older
Depleted iron stores	< 12	< 15
Depleted iron stores in the presence of infection or inflammation	< 30	< 30

WHO proposed to raise the ferritin cut-off defining iron deficiency to 30 µg/L to account for the increase in ferritin concentration caused by inflammation (55). Transferrin saturation (Tfs) levels present also a small but non-significant increase with age, but there are no gender differences (56).

Use of new alternative markers for iron status in pediatric IBD

sTfR : In adults, the soluble transferrin receptor concentration provides a sensitive measure of iron depletion. In children, low serum ferritin and iron concentrations, even within the normal physiologic range, results in high TfR concentrations. The lower the iron stores the stronger the influence of ferritin on TfR (57). Median sTfR value (1.50) and reference intervals in children aged 6-10 years (0.93-3.00) were higher than in adults (0.9-2.3 mg/l). sTfR alone can not be used to discriminate in border-line situations between normal and iron deficient patients (58). To improve sensitivity Jain et al used the sTfR/log ferritin ratio in children, where a cut off > 2.55 stands for IDA and < 2.55 or ACD (59).

Reticulocyte hemoglobin content (CHr) : reticulocyte indices may allow a real-time evaluation of iron deficient erythropoiesis and of the effectiveness of iron replacement therapy (60).

Hepcidin : Normal values have been described for children (mean = 40.8 ng/ml, SD = 13.9) (61). In the prepubertal child there is no difference according to gender, however, postpubertal girls have a significantly lower hepcidin concentration than males. Hepcidin may present a useful tool to discriminate IDA from ACD in the future (61).

Treatment of anemia in pediatric IBD

Based upon the scarce descriptive reports, response to treatment with oral and IV iron seems to be similar in adults, adolescents and children.

Oral iron treatment should aim at a supplement of 3 mg elemental iron/kg/day. For older children > 25 kg, ferrous fumarate tablets are available, for younger children a ferri polysacharaat complex (drops) and ferrogluconate for children > 14 kg are available. Side effects are nausea, vomiting, diarrhea, constipation, abdominal pain and anorexia.

Various intravenous iron products are currently available with differences in biochemical characteristics, side effects and dosing (26). High molecular weight iron dextran is obsolete, because of its potential to cause severe anaphylactic shock and associated mortality (62). The newer formulations like iron sucrose and iron carboxymaltose have a very assuring safety profile. Of these formulations ferric carboxymaltose has the major advantage of safe administration in a single dose. Ferric carboxymaltose is used off-label in children younger than 14 years of age. It is given in a single IV dose with a maximum of 15 mg/kg bodyweight up to 500 mg/week, when diluted for infusion the maximum dose is 20 mg/kg bodyweight with a maximum of 1000 mg/week. In children < 35 kg the maximum dose per week is 500 mg.

The dose of iron sucrose is still calculated with the Ganzoni formula (total body iron deficit in mg = (body weight in kg× [target hemoglobin - actual hemoglobin in g/dL]×0.24)+ iron depot (= 15 mg/kg with maximum of 500 mg)). Iron sucrose is given in a maximum of 200 mg/day, no more than 3 times a week.

Specific considerations for anemia in pregnant IBD patients

A healthy pregnancy is associated with a modest decrease in hemoglobin levels, due to a greater expansion of plasma volume relative to the increase in RBC mass. The lowest hemoglobin level is measured in the late second to early third trimester. WHO and the Center for Disease Control and Prevention have defined anemia as hemoglobin levels of less than 11 g/dl in the first and third trimesters and less than 10.5 g/dl in the second trimester (27).

Serum ferritin is of limited use in diagnosing iron deficiency during pregnancy as concentrations fall during late pregnancy, even when bone marrow iron is present (63).

Pregnancy itself is not only influencing diagnostics for anemia, but also has an influence on the metabolism of maintenance therapy of IBD itself. Several studies have demonstrated a favourable safety profile for thiopurine use during pregnancy. However, pregnancy has a major effect on maternal thiopurine metabolism. In utero, the unborn child is exposed to 6-TGN, but not to 6-MMP. In a small and uncontrolled study, 60% of the infants were born with anaemia, which raises the question whether infants should be tested for possible anaemia immediately after birth (64).

It is of great importance that iron deficient women are treated during pregnancy. Especially in view of evidence that iron deficiency causes a delayed growth and development of the fetus and an increase in behavioral problems later in childhood (65).

Since most (healthy) women do not have adequate iron stores to handle the demands of pregnancy, iron is commonly prescribed as part of a prenatal multivitamin.

IV iron sucrose and iron carboxymaltose can be used to treat iron deficient anemia in the second and third trimester. Iron deficiency occurring in the first trimester of pregnancy can in many cases be treated with oral iron. Furthermore, there are no safety data on the use of IV iron in the first trimester.

General conclusion

Every patient with IBD, whether adult or child, should be regularly checked for the presence of anemia, as this extraintestinal manifestation is very common, affects the quality of life of the patient and, in most cases, is easily manageable. In case of iron deficiency anemia, the recommended route of iron administration is dependent on the severity of the anemia and the IBD activity.

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Addendum

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

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