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Management of inflammatory bowel disease-related anaemia and iron deficiency with specific reference to the role of intravenous iron in current practice

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Abstract

Introduction: Anaemia is a common extraintestinal manifestation in patients with inflammatory bowel disease, impacting disease prognosis, morbidity, hospitalisation rates and time lost from work. While iron deficiency anaemia and anaemia of chronic inflammation predominate, combinations of haematimetric and biochemical markers facilitate the diagnosis and targeted therapy of other aetiologies according to their underlying pathophysiological causes. Intravenous iron replacement is currently recommended in IBD patients with moderate to severe anaemia or intolerance to oral iron.

Areas covered: This review examines the impact, pathophysiology and diagnostics of iron deficiency and anaemia, compares the characteristics and safety profiles of available oral and intravenous iron preparations, and highlights issues which require consideration in decision making for therapy administration and monitoring.

Expert opinion: Modern intravenous iron formulations have been shown to be safe and effective in IBD patients, allowing rapid anaemia correction and repletion of iron stores. While traditional oral iron preparations are associated with increased inflammation, negative effects on the microbiome, and poor tolerance and compliance, first clinical trial data indicate that newer oral compounds such as ferric maltol and sucrosomial iron offer improved tolerability and may thus offer a viable alternative for the future.

Keywords

Anaemia, Inflammatory bowel disease, deficiency

Article Highlights:

- Iron deficiency aenemia is the most common systemic complication and extraintestinal manifestation of inflammatory bowel disease.

- There is growing evidence to suggest that an adequate iron supply is essential not only to avoid anaemia, but also to maintain a good quality of life, and it is becoming apparent that iron deficiency merits treatment per se, even in nonanaemic patients.

- Common biochemical parameters are an inadequate basis for the assessment of iron status in patients who have an inflammatory condition such as IBD.

- Results from several RCTs showed that intravenous iron therapy improved quality of life in significantly more patients than oral iron, even in the absence of anaemia.

- Physicians now have a wider choice of intravenous iron preparations than ever before. The structures of new preparations permit far larger doses of iron to be administered safely in a single visit, an important aspect for IBD patients.

Abbreviations

ACI, anaemia of chronic inflammation; CHr, reticulocyte haemoglobin; CRP, c-reactive protein; ECCO, European Crohn's and Colitis Organisation; FGF-23, fibroblast growth factor; IBD, inflammatory bowel disease; IDA, iron deficiency anaemia; iFGF-23, intact FGF-23; MCV, mean corpuscular volume; RBC, red blood cell; sTfR, soluble transferrin receptor; TfR/F, transferrin-ferritin ratio; ZPP, zinc protoporphyrin; %HYPO, percentage of hypochromic red cells.

1. **Introduction**

Iron deficiency is increasingly widely recognised as the most frequent systemic complication and extraintestinal manifestation of inflammatory bowel disease (IBD). Iron deficiency is caused by various factors directly or indirectly related to IBD[1, 2]. Depending on characteristics of the respective study populations (e.g. in-/outpatient, gender, age at diagnosis, active/inactive disease), iron deficiency with or without anaemia has been reported to affect 13%-90% of patients with IBD[3-6,7, 8,9,10,11,12].

ID, even without manifest anaemia, can substantially impact IBD patients' quality of life (QoL), affecting physical, cognitive and emotional functions, ability to work, hospitalisation rates and duration, and healthcare costs[13, 14]. The most common symptoms of anaemia include paleness, fatigue, dyspnoea, headache, restless legs syndrome, alopecia, atrophic glossitis, cardiac murmur and tachycardia[15]. Thus, IBD-associated anaemia and iron deficiency require appropriate diagnostic and therapeutic management[16].

While the two major aetiologies are iron deficiency anaemia (IDA), and anaemia of chronic inflammation (ACI), IBD-associated anaemia is frequently a classic example of combined IDA and ACI[17]. Nevertheless, IBD patients should be screened for alternative origins of anaemia, including vitamin B_{12} or folate deficiency, or long-term drug intake (sulfasalazine[18], thiopurines[19], methotrexate[20], calcineurin inhibitors[21]).

In IBD patients, IDA results not only from insufficient iron intake, but also from blood loss caused by ulceration of the bowel wall (especially in ulcerative colitis) and deficient intestinal iron absorption in the presence of inflammation (for review, see[17]). The inflammatory cytokines, IL-1, IL-6, and oncostatin M are known to disrupt intestinal iron absorption via hepcidin-induced ferroportin degradation, independent of the underlying type and location of IBD[22]. Moreover, *in vitro* and *in vivo* studies have demonstrated tumour necrosis factor to inhibit duodenal iron absorption via a hepcidin-independent mechanism involving tumour necrosis factor-induced iron storage within ferritin in enterocytes[23, 24].

Anaemia of chronic inflammation (ACI)[25] is characterised by mild to moderate anaemia,

normal to diminished mean corpuscular volume (MCV), reduced serum iron, normal to elevated serum ferritin, and increased reticuloendothelial system stores relative to total body iron, in patients with chronic infection, inflammatory disease or malignancy[26]. Growing understanding of its molecular mechanisms suggest that ACI derives from a combined action of hepatocyte- and macrophage-derived hepcidin and inflammatory cytokines (for review, see[27, 28]).

2. **Diagnosing anaemia and iron deficiency in IBD**

Current ECCO guidelines[16, 29] recommend anaemia workup in IBD patients if haemoglobin is below normal levels, as defined by the WHO (Hb ≥12g/dL in women and ≥13g/dL in men). Minimum workup should include red cell distribution width and mean corpuscular volume (MCV), reticulocyte count, differential blood cell count, serum ferritin, transferrin saturation (TSAT) and C-reactive protein (CRP)[16, 30]. In a more comprehensive workup, additional parameters include serum vitamin B_{12}, folic acid, haptoglobin, percentage of hypochromic red cells (%HYPO), reticulocyte haemoglobin (CHr), lactate dehydrogenase, soluble transferrin receptor (sTfR), zinc protoporphyrin (ZPP), and creatinine (Table 1).

2.1 Diagnosing IDA and ACI

In IBD patients, reliable diagnosis of IDA or ACI using only traditional biomarkers can be problematic, not least due to confounding influences of concomitant chronic illness and/or medications. While MCV and mean corpuscular haemoglobin (MCH) are useful parameters which are routinely determined in IBD patients within the complete blood count, MCV is often slow to decrease in the early stages of anaemia and/or moderated by concomitant nutrient deficiencies (e.g. folic acid, vitamin B_{12}) or drugs (e.g. azathioprine, methotrexate)[17].

In clinical practice, iron status is assessed primarily on the basis of serum ferritin levels, if at all. However, not only are serum ferritin levels gender-specific, but ferritin is an acute-phase protein and thus prone to false elevation or normalisation when inflammation is present (e.g.

hepcidin-mediated iron sequestration in chronic inflammatory disease)[31]. Alongside inflammation markers (CRP, ESR), anaemia workup should therefore include transferrin saturation, a marker of iron availability for haematopoiesis that is less influenced by inflammatory reactions[17, 31] but currently tested in only 25% of anaemic IBD patients[17].

Reticulocytes are immature erythrocytes whose ribosomal RNA can be microscopically detected using specific alkaline stains and their fraction in the blood count determined by flow cytometry at reasonable cost. In chronic, constant anaemia, relative reticulocyte count correlates inversely (but non-linearly) with erythrocyte lifespan curtailment. The absolute reticulocyte count is a marker of effective erythrocyte production by the bone marrow. A low or normal reticulocyte count indicates an ineffectual response to anaemia resulting from inapposite erythropoiesis owing to micronutrient deficiencies or primary bone marrow disease (=> hyporegenerative anaemia, Figure 1a). Increased reticulocyte numbers denote heightened erythropoiesis (e.g. due to bleeding or haemolysis), thus excluding micronutrient deficiencies (=> hyperregenerative anaemia, Figure 1b). The reticulocyte production index (RPI) indicates change in erythrocyte production relative to the normal value, representing the relative reticulocyte count (RTC, %) corrected to anaemia severity (patient's haematocrit [HCT-P] in relation to ideal haematocrit [HCT-N = 0.45] and reticulocyte maturation time [RMT]): RPI = (RTC [%] x HCT-P)/(HCT-N [0.45] x RMT)[32].

Increased migration of *soluble transferrin receptors (sTfR)* from cells into the plasma reflects erythropoietic activity and inversely correlates with the quantity of iron available for erythropoiesis[33]. Thus, sTfR was presumed a useful indicator of iron-deficient erythropoiesis. However, studies in other inflammatory conditions have shown sTfR to have limited value as a marker of coexistent functional iron deficiency[34, 35]. Nevertheless, sTfR-ferritin (TfR/F) ratio may be a useful clinical marker for anaemia when combined with other haematologic parameters such as reticulocyte haemoglobin content (see below)[36].

Two studies have examined the accuracy of the TfR/F ratio in IBD patients[37, 38]. Oustamanolakis et al. demonstrated high accuracy of TfR/F (cutoff >1.4) for IDA diagnosis, independent of CRP levels and/or disease activity (sensitivity 91%, specificity 92%)[37]. Abitbol et al., defining a higher cutoff (TfR/F ratio >2), validated TfR/F as a useful clinical marker for true iron deficiency in an IBD population[38]. Unfortunately, since its determination is costly and cutoff levels assay-dependent, TfR/F index cannot currently be recommended for routine diagnostics in primary anaemia screening. It may nevertheless be a useful additional marker when ferritin values are elevated in the presence of inflammation[38]. Notably, however, sTfR concentration increases in every expansion of erythropoiesis (i.e. haemolytic anaemia, thalassaemia, polycythaemia) and is reduced in aplastic anaemia and other conditions with hypoproliferative erythropoiesis (e.g. renal anaemia).

Cytometry of *reticulocyte haemoglobin content (CHr)* and *percentage of hypochromic red cells* (%HYPO) have shown high predictive value in differential diagnosis of IDA, independent of inflammation and ACI[39, 40]. While a decrease in %HYPO (mean lifespan, 120 days) indicates insufficient long-term iron supply, diminished CHr (mean lifetime, 48h) signifies current deficit, reflecting iron bioavailability over the previous 3–4 days. CHr is also a proven early marker for treatment response to iron supplementation[41]. However, since %HYPO is a factor of total red blood cell (RBC) count, which is sensitive to storage time, samples must be processed locally.

Zinc protoporphyrin (ZPP) was identified in 1966 by Dagg and colleagues as a potential marker of ID[42]. When iron supply is inadequate for erythropoiesis, zinc, instead of iron, is incorporated into protoporphyrin IX. Thus, ZPP concentrations (normal value <40µmol/mol haem) inversely correlate with iron status in the bone marrow during erythropoiesis, making ZPP an effective indicator of ID, independent of inflammatory activity. Concentrations of >80µmol/mol haem are associated with manifest ID, while 40–80µmol/mol haem represent latent iron deficiency (haemoglobin normal). In severe cases, ZPP values as high as 1000µmol/mol haem have been reported[43]. ZPP concentration is thus a reliable marker of functional iron deficiency and a useful alternative to %HYPO or CHr, although it is less

sensitive to acute variations in iron availability. For determination of functional iron deficiency, measurements must be made on washed RBCs, applying appropriate cutoffs. Only recently, two studies demonstrated the usefulness of zinc protoporphyrin/haem ratio as an accurate clinical parameter for IDA screening in IBD patients [44, 45].

While research into the possible utility of *hepcidin* determination in anaemia diagnostics is not yet conclusive, preliminary data indicate that it may be a potent predictor of intestinal iron incorporation[46]. These results have recently been confirmed in a paediatric IBD study[47]. Thus, serum hepcidin seems to be a sensitive surrogate marker to identify IBD patients who might benefit from oral iron replacement, once accurate and feasible assays have been developed and uniform standard cutoffs ascertained.

3. Treatment of anaemia and iron deficiency

Identification of the anaemia type and treatment of its underlying causes are prerequisites to effective therapy. Depending on the aetiology of anaemia, treatment is also based on micronutrient supplementation with iron, vitamins B_6, B_{12} and D, and/or folate.

ECCO guidelines recommend that oral or intravenous iron therapy is initiated in IBD patients as soon as IDA is diagnosed or deemed likely due to ambiguous results for iron markers. iron deficiency without manifest anaemia requires an individualised approach. The therapeutic goal of iron replacement in IDA is to increase haemoglobin levels by >2g/dL or to normal levels within 4 weeks, replenish body iron stores, relieve anaemia symptoms, and thus improve QoL[16]. Recent ESPEN guidelines[48] concur largely with those of ECCO.

Intramuscular iron is now considered obsolete, since injections are painful and cause unnecessary tissue damage and unacceptable side effects[16]. The supplementation route should be determined according to symptoms, aetiology and severity of iron deficiency and/or anaemia and dynamics of haemoglobin decrease, and taking account of comorbidities and individual risks associated with therapy.

3.1 Oral iron supplementation

Oral iron supplementation is generally considered standard first-line therapy in IDA. However, although convenient and relatively inexpensive, oral iron is often ineffectively absorbed and consequently poorly tolerated by IBD patients, eliciting gastrointestinal side effects such as pain, nausea, flatulence, diarrhoea and gastric erosion[49], particularly in elderly patients[50]. Consequently, up to 50% of IBD patients prematurely discontinue oral iron therapy[49, 51]. Although oral iron preparations have been shown to sufficiently increase haemoglobin levels, 3-6 months' additional treatment may be necessary before iron stores are replete and serum ferritin normalised[52].

Recent clinical studies have confirmed findings in rodent models showing that non-absorbed oral iron shifts the composition of the gut microbiota, increasing the concentration of intestinal pathogens and thereby promoting intestinal inflammation and carcinogenity (see review[53]). Interestingly, although some studies of oral iron supplementation in adults report worsening disease activity symptom scores[54-56], others do not[14, 57]. As yet, no clinical trial data show a consistent increase in inflammatory markers in IBD patients treated with oral iron. However, two recent studies in African children without IBD[58, 59] demonstrated that oral iron supplementation for 4–6 months is associated with a rise in faecal calprotectin. It may therefore be assumed that pro-inflammatory effects of oral iron supplementation, whether due to its oxidant action or to ensuing changes in the gut microbiome, or a combination of both, take longer than the typical trial observation period of 6–8 weeks to become apparent. This may be especially relevant for IBD patients needing prolonged or repeated courses of oral iron to maintain serum haemoglobin levels.

The two main oral iron compounds comprise ferrous (Fe^{2+}) or ferric (Fe^{3+}) salts (Table 2). Numerous formulations, including amino-acid chelates, polysaccharide-iron complex, carbonyl iron, extended-release products and combination products, are also available. Characteristics of the different oral iron formulations are shown in Table 3. While head-to-head studies of ferrous vs. ferric salts are lacking, their efficacy and safety in IBD patients are presumed

comparable. Due to the poor solubility of ferric iron compounds, Fe^{2+} salts (e.g. iron sulphate, gluconate, fumarate), are more commonly used.

In view of the limited rate of intestinal iron absorption, a typical therapeutic oral iron dose of, for example, 100mg elemental iron, far exceeds the amount that can be actively absorbed. In this situation, due to the physicochemical properties of ferrous salts, passive uptake occurs via the paracellular route, allowing a dose-related portion of Fe^{2+} to directly enter the blood[60, 61]. Under the pressure of passive diffusion, however, transferrin in the blood, normally approximately one-third saturated, becomes fully saturated. As a result, non-transferrin-bound iron (NTBI) increasingly circulates in the plasma and, weakly bound to albumin and other proteins, is taken up via an unregulated mechanism involving endocrine, pulmonary and heart cells, resulting in the formation of reactive oxygen species, thus inducing oxidative stress[62]. With rapidly absorbed preparations, non-transferrin-bound iron can be detected even before transferrin is fully saturated. Figure 2 demonstrates the quantification of non-transferrin-bound iron in serum samples from adults with normal iron stores after oral administration of 100mg ferrous iron. Despite transferrin saturation remaining below 100%, increased non-transferrin-bound iron concentrations were observed within four hours of dosing. Significant levels of non-transferrin-bound iron were detected even at lower doses, e.g. 10mg iron as ferrous ascorbate or ferrous glycine sulphate[61, 62].

In an attempt to minimise adverse events associated with ferrous salts, more slowly-absorbed preparations (e.g. ferrous fumarate) have been developed, characterized by low solubility and a slow dissolution rate after oral administration[63]. In effect, the release rate of ferrous ions is slower from ferrous fumarate than from the highly soluble ferrous sulphate. Despite the slower iron absorption and lower AUC values observed with the slow-release formulation, Kaltwasser et al. demonstrated that standard or slow-release preparations (in this case, ferrous sulphate) exhibit iron bioavailability comparable to iron sulphate[64]. Comparative data from IBD patients are lacking.

As a second strategy, more stable sugar iron(III) complexes such as iron(III)-polymaltose and iron(III)-trimaltol, showing only minimal paracellular uptake, have been developed.
The non-ionic iron(III)-polymaltose complex is made of non-ionic iron(III) in the form of polynuclear iron(III)-hydroxide and polymaltose ligands. The resulting complex is stable. Being in a non-ionic form, the iron neither interacts with food constituents nor does it induce the generation of reactive oxygen species. Thus, Schuman et al. demonstrated oral administration of ferrous sulphate, but not iron polymaltose, to effect a substantial increase of non-transferrin-bound iron in healthy iron-adequate adults with marginal iron stores[65, 66]. Iron(III)-polymaltose has also been shown to be better tolerated than ferrous sulphate in IBD patients with IDA[55]. However, efficacy data are conflicting[67] or, in the case of IBD, lacking.

Ferric maltol (syn. ST10, ST10-021, ferric tri-maltol, tris-maltol-iron(III), tri-maltol-iron(III), ferric (3-hydroxy-2-methyl-4-pyrone)) is a complex of a single ferric ion (Fe3+) chelated with high affinity to three maltol (3-hydroxy-2-methyl-4-pyrone) molecules. As in iron polymaltose, maltol prevents the formation of iron hydroxide polymers and renders the iron available for absorption while stabilised in the ferric form[68].

By contrast to iron(III)-polymaltose, an early clinical trial reported oral ferric maltol to be effective in patients intolerant to oral ferrous sulphate[69]. A recent randomised placebo-controlled trial including adult patients with quiescent or mild-to-moderate ulcerative colitis or Crohn's disease and mild-to-moderate IDA demonstrated that ferric maltol is effective in IBD patients unresponsive or intolerant to ferrous sulphate[70]. In addition, data published from the long-term extension of a phase III study demonstrated that ferric maltol was well tolerated throughout a 64-week period[71].

A new highly bioavailable oral liposomal iron formulation, sucrosomial iron, has only recently been launched in Europe. Sucrosomial iron is a preparation of ferric pyrophosphate conveyed and protected by a phospholipid and sucrester matrix. Studies demonstrating its non-inferiority

to intravenous iron gluconate in anaemic cancer and CKD patients also showed favourable tolerability and safety results. Studies in the IBD population are warranted[72, 73].

In conclusion, polysaccharide iron complexes and liposomal iron formulations have become available as alternative therapies, offering improved absorption and tolerability compared to traditional iron salts. However, they are significantly more expensive than iron salts.

Dosing and switch from oral to intravenous iron

The recommended daily dose for oral iron supplementation is 100–200mg elementary iron for adults and 3–6mg/kg body weight (divided into two doses) for children[52]. However, data of Moretti et al.[74] recently confirmed that in women with depleted iron stores, iron absorption is highest at lower iron doses (40-80mg). More importantly, the study demonstrated that low-dose iron given on alternate days may maximise fractional iron absorption, increase dosage efficacy, reduce gastrointestinal exposure to unabsorbed iron, and ultimately improve tolerance of iron supplements. Their findings emphasise the need to study longer-term, alternate-day schedules for iron supplementation in IBD patients[74].

After normalisation of haemoglobin levels, oral iron supplementation must persist for at least 3 months to completely replenish iron stores[75]. Since even after two months' treatment, adherence has been estimated to be only 10%-32%, this is likely to diminish even further over a longer course of treatment[76].

Optimal timing for a switch from oral to intravenous iron replacement therapy is not well characterised in patient care or treatment algorithms. Okam et al. undertook a secondary data analysis of five randomised controlled trials, and concluded that a haemoglobin increase of ≥1.0g/dL at day 14 after commencement of oral iron replacement may be the most accurate predictor of sustained treatment response, with a sensitivity of 90.1%, a specificity of 79.3% and a positive predictive value of 92.9%. The authors conclude that in clinical practice, nonresponders (i.e. haemoglobin increase <1.0g/dL at day 14) should be switched to intravenous iron[77]. However, prospective clinical trials are warranted to increase the level of evidence before this recommendation can be incorporated into treatment guidelines.

3.2 Intravenous iron supplementation

The superior efficacy of intravenous iron over oral iron for the treatment of IDA in IBD has already been shown in three separate meta-analyses[78-80]. Moreover, intravenous iron replacement facilitates the faster correction of iron deficiency and repletion of body iron stores; for example, applying the Ganzoni formula, the total iron requirement for a male patient weighing 75kg is 1,500mg. Based on a daily iron absorption of 12-15mg and assuming a high level of adherence and no further bleeding or concomitant inflammation, oral iron intake would need to continue for 4-5 months. Furthermore, intravenous administration has been found to achieve higher ferritin levels than oral iron, thus possibly reducing the likelihood of anaemia recurrence in the long term. Although intravenous iron is costlier than oral treatment, administration by a medical professional ensures compliance and more reliable repletion of iron stores, at least when single higher doses of iron are given[81].

Currently, six intravenous iron formulations are available for treatment of IDA (Table 4): iron dextran, iron gluconate, iron sucrose, iron carboxymaltose, iron isomaltoside and ferumoxytol. While all intravenous iron preparations are made of iron-carbohydrate complexes composed of a spheroidal polynuclear iron(III)-oxyhydroxide/oxide core surrounded by a carbohydrate ligand which serves to stabilize the complex, they differ in core size and the type and density of the surrounding carbohydrate. Since iron must be released from the iron-carbohydrate complex to become available at its site of action, iron-carbohydrate complexes may be considered as prodrugs: after intravenous ferric carboxymaltose administration, iron-carbohydrate complexes are taken up into macrophages by an endocytic mechanism leading to endolysosomal degradation of the carbohydrate shell and the polynuclear iron, and the released Fe^{3+} is reduced to release Fe^{2+} (probably by the six-transmembrane epithelial antigen of the prostate 3 (STEAP3)). Subsequently, DMT-1 activity causes extrusion of Fe^{2+} from the endolysosomes to the cytosolic labile iron pool. Finally, depending on systemic iron need, it is extrused from the cytosol to the plasma by FPN (after oxidisation by hephestin and ceruloplasmin to Fe^{3+}) and transported by transferrin to the liver, bone marrow and other

tissues, or stored as ferritin. Iron from the labile iron pool may also be delivered to the mitochondria, probably via cytosolic iron chaperones (Figure 3). Dextran-coated iron oxide nanoparticles have also been proposed to be taken up by a receptor-mediated mechanism. In the case of ferric carboxymaltose, following intravenous administration, the carboxymaltose shell is partially degraded by the blood α-amylase[82].

In all intravenous iron preparations, the molecular size and type of carbohydrate ligand defining thermodynamic stability are responsible for ligand dissociation of the carbohydrate iron complex before endocytosis, resulting in the release of weakly-bound non-transferrin-bound iron. Consequently, oxidative stress induction may occur due to the nonselective uptake of non-transferrin-bound iron by highly vascular tissue. On this basis, iron formulations can be grouped into labile, semi-labile (iron sucrose, iron gluconate) and stable iron complexes (ferric carboxymaltose, iron isomaltoside, iron dextran)[83]. Thus, thermodynamic stability restricts both the maximum amount of iron solution that can be applied in a single dose and maximum infusion speed[63, 84].

Dosing of intravenous iron

Iron requirements have traditionally been calculated using the Ganzoni formula (iron deficit [mg] = body weight [kg] x (target Hb - actual Hb [g/dL]) x 2.4 + 500 mg)[85]. However, the formula is complex, inconvenient and inconsistently used, and tends to undercalculate iron requirements. A simpler fixed-dose regimen based on haemoglobin and body weight applied to ferric carboxymaltose dosing in IBD patients showed superior efficacy compared with iron sucrose dosing according to Ganzoni[86]. This simple dosing table (Table 5) now provides the basis for dosing recommendations for both ferric carboxymaltose and iron isomaltoside. For patients requiring fast and efficient iron replenishment, high-dosed ferric carboxymaltose and iron isomaltoside are generally favoured, since these formulations have been more comprehensively tested at high doses in clinical and observational trials.

Dosage recommendations for the different intravenous compounds vary considerably: While iron sucrose and low molecular weight iron dextran require more frequent, smaller one-hour

infusions of 100–200mg up to three times per week, ferric carboxymaltose can be given in weekly 15-minute applications of up to 1000mg or 20mg/kg BW, and for iron isomaltoside the recommended dose of 20mg/kg BW should be infused over ca. 15–30 minutes 1-3 times per week. High doses of iron sucrose gluconate can generate significant amounts of non-transferrin-bound iron, thus the maximum recommended single dose is lower[87]. Similarly, sodium ferric gluconate releases comparatively large amounts of iron into the circulation, resulting in non-transferrin-bound iron-associated oxidative stress. This necessitates application of small doses at a slow infusion rate to reduce the risk of acute liver toxicity and adverse events associated with increased transferrin saturation, e.g. metallic taste[63, 84].

Even after anaemia correction and iron store repletion, anaemia recurs in over 50% of IBD patients within 10-12 months[88]. However, the FERGImain and PROCEEDextend trials impressively demonstrated that the recurrence of IDA in IBD patients can effectively be prevented[89, 90]. Moreover, the suggested proactive approach, with regular monitoring of iron indices and prompt supplementation when iron stores begin to diminish, is evidentially cost-effective[16]. In IBD patients, haemoglobin and iron status markers (haemoglobin, ferritin, transferrin saturation, CRP) should be monitored every 3 months for at least one year after correction, and every 6-12 months after normalisation of haemoglobin and repletion of iron stores.

Adverse reactions associated with intravenous iron

The earliest intravenous iron preparations were associated with unacceptable acute toxicity resulting from the release of bioactive free iron. However, due to their improved thermodynamic stability, anaphylactic reactions to currently approved intravenous iron formulations are evidentially rare. Chertow et al. found absolute rates of life-threatening adverse reactions of 0.6, 0.9, 3.3 and 11.3 per million infusions for iron sucrose, sodium ferric gluconate complex, low molecular weight and high molecular weight iron dextran, respectively[91, 92]Recently, in a US Medicare nondialysis population, Wang et al. compared the risks of anaphylaxis associated with intravenous iron dextran, gluconate, sucrose, or

ferumoxytol and found iron sucrose to have the lowest and iron dextran the highest risk[93]. In another study, while high molecular weight iron dextran and ferric carboxymaltose were found to be similarly effective, ferric carboxymaltose was associated with fewer hypersensitivity reactions[94].

The ligands of ferumoxytol (carboxymethyl dextran) and iron isomaltoside 1000 (a very low molecular weight hydrogenated dextran of 3-5 glucose units) have been shown to cross-react with antidextran antibodies *in vitro*, possibly because the ligand acts as a polyvalent dextran when bound to polynuclear iron[63, 84]. Therefore, both should be used with caution in patients who have previously shown intolerance to iron dextran. In contrast, sodium ferric gluconate, iron sucrose and ferric carboxymaltose contain neither dextran nor derivatives thereof, and no similar *in vitro* reaction has been observed. Clinical data confirm that at least iron sucrose can be administered to patients who have previously reacted to iron dextran[95].

Since the manufacture of polynuclear Fe3+ oxyhydroxide compounds, especially iron sucrose, is complex, iron sucrose-similar (ISS) formulations may differ in terms of physicochemical characteristics and toxicological profiles compared to the originator, as confirmed by non-clinical studies examining oxidative stress and inflammatory responses to ISS formulations compared to the originator drug[96-98].

The *pathogenesis* of hypersensitivity reactions to intravenous iron may vary with the iron preparation used and pre-existing risk factors of the recipient. Nevertheless, the risk of hypersensitivity cannot be determined by their clinical presentation. Immunological IgE- and IgG-mediated responses associated with the dextran component may explain the higher frequency of anaphylactic reactions associated with high molecular weight iron dextran compared to non-dextran preparations[99]. As regards the other formulations, the most common mechanism is thought to be complement system activation triggered by iron nanocolloids which comprise all existing intravenous iron compounds, known also as complement activation-related pseudoallergy (CARPA). In CARPA, the triggered activation of mast cells and basophils causes a secretion response (e.g., thromboxanes, leukotrienes, histamines),

while smooth muscle contraction heightens capillary permeability and increases fluid loss from the intravascular space. Consequently, patients may suffer from tachycardia, laryngeal oedema, bronchospasm, hypo-/hypertension, hypoxia and insufficient tissue perfusion, and in severe cases hypersensitivity reactions, loss of consciousness, circulatory collapse, and cardiac and respiratory arrest[100-102].

While underlying mechanisms of hypersensitivity to intravenous iron are not yet entirely understood, asthma, mastocytosis, atopic status and concomitant medications (e.g., beta-blockers or angiotensin-converting enzyme inhibitors) are possible risk factors[100-102]. The management of hypersensitivity reactions to intravenous iron depends on their severity (Table 6).

The 2013 Assessment Report of the European Medicines Agency (EMA)[103] reviewed risks associated with all intravenous iron-containing medicinal products registered in the European Union. The report concludes that the risk-benefit ratio of all approved intravenous formulations for treatment of iron deficiency continues to be favourable for patients who respond insufficiently or show intolerance to oral iron. Subsequently, EMA no longer prescribes a test dose of intravenous iron, but continues to stipulate that resuscitation facilities and staff trained to evaluate and manage anaphylactic or anaphylactoid reactions must be immediately available when intravenous iron is administered.

Intravenous iron-induced hypophosphataemia and effects on bone metabolism

Intravenous iron-induced transient hypophosphataemia is a well-documented side-effect of intravenous iron therapy first described in 1982 in a patient receiving repeated infusions of saccharated iron oxide[104]. Clinical trial data suggest that ferric carboxymaltose is associated with the highest risk for hypophosphataemia occurrence, followed by iron polymaltose, iron sucrose and iron isomaltoside 1000. Reasons for this difference are unclear. A post-hoc analysis of 81 patients given ferric carboxymaltose or iron isomaltoside for gastroenterological conditions including IBD[105] compared electrolyte and metabolic parameters before and after intravenous treatment. Twenty-six patients developed post-treatment hypophosphataemia

(defined as <0.8mmol/L). In the subpopulation with data available concerning fibroblast growth factor (FGF-23), those with hypophosphataemia showed a significant rise in intact FGF-23 (iFGF-23) both versus baseline and versus patients with normal serum phosphate levels; biologically inactive (c-terminal) cFGF-23 levels were similar. While the underlying mechanisms are not fully understood[106], limited data suggest the hypophosphataemic effect of ferric carboxymaltose to be possibly dose-dependent. However, it is unclear whether this association relates to total iron dose or treatment duration.

Severe phosphate depletion may cause fatigue, myocardial depression, rhabdomyolysis and haemolytic anaemia[107, 108], and can ultimately contribute to bone abnormalities such as rickets[109, 110]. Rarely, severe hypophosphataemia can be fatal, due to respiratory muscle dysfunction or impaired myocardial metabolism and decreased cardiac contractility[111, 112]. Effects on bone metabolism have been observed only as sequela to several years' high-dose intravenous iron therapy. Nevertheless, in view of the potentially severe consequences of hypophosphataemia, where prolonged, high-dose ferric carboxymaltose therapy is applied in chronic conditions, serum phosphate should be routinely monitored. On commencement of ferric carboxymaltose therapy, patients with pre-existing low phosphate levels or disorders which interfere with phosphate metabolism also warrant closer monitoring, while common underlying conditions such as vitamin D deficiency should be routinely managed. Whereas the highest incidences and most severe manifestations of hypophosphataemia have been reported in patients whose underlying cause of iron deficiency cannot be corrected, impaired renal function has been shown to be protective[104].

As yet, no evidence-based recommendations on hypophosphataemia management have been issued. Most experience of hypophosphataemia has been gained in critically ill patients. Mild hypophosphataemia (<LLN–2.5mg/dL; <LLN–0.8mmol/L)[113] is usually asymptomatic. Mild or moderate hypophosphataemia (<2.5–2.0mg/dL; <0.8–0.6mmol/L)[113] of short duration generally does not require treatment. Prolonged moderate or severe hypophosphataemia should prompt treatment of the underlying cause, and is usually treated by phosphate supplementation either

orally or intravenously as sodium hydrogen phosphate. Severe (<2.0–1.0mg/dL; <0.6–0.3mmol/L)[113] or potentially life-threatening hypophosphataemia (<1.0mg/dL; <0.3mmol/L)[113] should be corrected with 50mmol parenteral sodium glycerophosphate or glucose-1-phosphate over 24 hours[109, 112]. Since FGF23 effects on vitamin D metabolism may complicate iron-induced hypophosphataemia, supplementation with calcitriol or alfacalcidiol is recommended[104].

Efficacy and safety of intravenous iron supplementation in IBD

Intravenous iron has been demonstrated to be safe, effective and well tolerated in the IBD population, allowing rapid correction of iron deficiency and repletion of body iron stores, whilst avoiding common side effects of oral iron supplementation by bypassing the gastrointestinal tract. In addition, intravenous iron replacement achieves a greater increase in ferritin levels than oral supplementation, thus possibly reducing the probability of subsequent anaemia recurrence[16].

The preponderance of published evidence indicates that all approved formulations of parenteral iron (low molecular weight iron dextran, ferric gluconate, ferumoxytol, iron sucrose, iron isomaltoside, ferric carboxymaltose) are safe and effective[114].

However, there are theoretical reasons why intravenous iron could worsen cardiovascular outcomes through increased oxidative stress, and there are concerns about its potential to exacerbate infections. None of these concerns could be borne out in clinical trials[114]. While in other patient groups, especially in an inpatient setting, repeated low-dose infusions may be unproblematic, single high-dose infusions may present a better option in IBD patients. Single total-dose infusions have been demonstrated to be safe and effective for low molecular weight iron dextran, ferumoxytol, iron isomaltoside and ferric carboxymaltose. Single total-dose infusions offer several advantages, including fewer intravenous lines, a lower cumulative risk of infusion reactions or extravasations, a reduction in office visits and deployment of medical personnel, and greater convenience for physicians and patients.[114]

For iron sucrose, iron dextran, ferric carboxymaltose and iron isomaltoside 1000, large trials demonstrate a good efficacy and safety profile in IBD patients in relation to dosage (1000mg or ≤20mg/kg body weight) and therapy duration (for review see[12, 81, 115]). In a systematic review and meta-analysis including 103 trials, Avni et al[78] reported an acceptable safety profile for intravenous iron and higher adherence rates for intravenous compared to oral iron, along with a better haemoglobin response and significant increases in ferritin and haemoglobin levels. Moreover, intravenous iron had no negative impact on disease activity indices. Similarly, Lee et al[80] found that while parenteral iron therapy achieved a slightly greater improvement in haemoglobin values compared with oral iron, serum ferritin levels clearly favoured intravenous over oral iron therapy. Moreover, intravenous iron was associated with fewer adverse events.

Having established that intravenous iron is safe and more effective than oral supplementation, and having also ascertained that different intravenous iron compounds have different structural, and thus thermodynamic, properties, the question arises as to which parenteral iron product, if any, should be favoured in an IBD population. Only recently, Aksan et al[116]. published the first systematic review and network meta-analysis to compare the efficacy and safety of different intravenous iron preparations in IBD patients. All formulations included in the analysis, i.e. low molecular weight iron dextran, iron sucrose, iron isomaltoside and ferric carboxymaltose, were found to be safe and effective for IDA treatment in patients with IBD. A rank probability matrix indicated ferric carboxymaltose to be the most effective intravenous iron formulation, on the available evidence, followed by iron sucrose. In addition, while all intravenous preparations were more effective than oral iron, this difference was statistically significant only for ferric carboxymaltose. Further trials are warranted to increase the evidence level concerning the comparative efficacy of different intravenous iron compounds in IBD patients with anaemia.

To date, no prospective data have been published concerning long-term outcomes of intravenous iron in IBD patients. However, large trials have been performed in oncology and nephrology populations; Kalantar-Zadeh et al[117] examined time-dependent associations

between intravenous iron (iron gluconate, iron sucrose, iron dextran) administration and both all-cause and cardiovascular mortality using prospective data of a two-year historical cohort of 58,058 maintenance haemodialysis patients. The lowest all-cause and cardiovascular death risks were associated with high ferritin (200-1200ng/dL), high serum iron (200-1200mcg/dL) and low transferrin saturation (30%-50%) levels. The authors concluded that the association between serum ferritin levels >800 ng/mL and mortality in patients on maintenance haemodialysis was largely associated with the confounding influence of malnutrition-inflammation-cachexia (wasting) syndrome. In addition, they found that intravenous iron administration of up to 400mg/mo was associated with improved survival[117]. Feldman et al[118] found no association between any level of intravenous iron administration and mortality with multivariate models in haemodialysis patients. Beguin et al[119] reported similar results in oncology patients with or without intravenous iron at >1500 days. While these studies suggest that long-term intravenous iron administration is safe, there remains a need for large, prospective studies in IBD patients.

Studies evaluating the cost-effectiveness of intravenous iron preparations

Nowadays, the cost-effectiveness of every new therapy is of paramount importance. While several studies have focused on the pharmacoeconomics of ferric carboxymaltose, data concerning other intravenous iron compounds are lacking. Bhandari[120], in a comparative analysis of hospital costs, reported that ferric carboxymaltose was less expensive than either iron sucrose or low molecular weight iron dextran, while Calvet et al.[121] found ferric carboxymaltose to have a lower cost impact versus iron sucrose, bearing in mind indirect costs, costs of the iron solution, staff, infusion devices and nonmedical direct costs.

In a Greek study, Fragoulakis et al. evaluated relative costs of ferric carboxymaltose, iron sucrose, and low molecular weight iron dextran in the management of IDA. The total cost of ferric carboxymaltose treatment in 100 inpatients was found to be 113% and 15.4% lower versus iron sucrose and low molecular weight iron dextran, respectively. In outpatients,

comparative cost savings of ferric carboxymaltose were even greater (201.1% and 151.8%, respectively).

Bager and Dahlerup evaluated healthcare costs in 111 Danish IBD outpatients treated with intravenous iron. Due to the lower number of outpatient visits required for equivalent treatment, and shorter infusion duration, ferric carboxymaltose was found to be clearly more cost-effective than iron sucrose, with higher drug costs outweighed by the higher administrative costs and time lost from work associated with iron sucrose[122]. Based on data from the FERGIcor trial, a randomized controlled trial comparing the safety and efficacy of iron sucrose and ferric carboxymaltose in IBD patients, Evstatiev et al. calculated a saving of 238€ for each single dose for ferric carboxymaltose[86].

3.3 Erythropoiesis-stimulating agents and blood transfusion

In the majority of patients with IBD, treatment of the underlying inflammatory condition, together with adequate iron (and vitamin) substitution is sufficient to correct anaemia. Erythropoiesis-stimulating agents are an option in patients with ACI who respond insufficiently to intravenous iron supplementation despite effective IBD control. Patients treated with erythropoiesis-stimulating agents have been shown in several trials to respond with a significant increase in haemoglobin levels and significant enhancement in QoL[123]. A recent systematic review confirmed administration of erythropoiesis-stimulating agents as adjunctive therapy to intravenous iron to be safe and effective, improve haematopoietic response, reduce transfusion need and improve haemoglobin levels. The combination also appears to be well tolerated. To minimize the risk of thromboembolic and/or cardiovascular events, maximal target haemoglobin value when administering erythropoiesis-stimulating agents should be limited to 12g/dL in patients with cancer or renal insufficiency[124].

Red blood cell (RBC) transfusion should generally be considered only when haemoglobin concentration is 7g/dL, in the presence of severe comorbidities or other individual risk factors, or when facing a life-threatening situation[16]. An increasing pool of evidence now underlines the

considerably increased risks of post-operative mortality and morbidity following blood transfusion. Indeed, Murphy et al. showed transfusion even of a single RBC unit to be associated with an adverse clinical outcome[125]. Furthermore, transfusions do not offer a long-term solution to anaemia, nor are they sufficient to replenish iron stores. Therefore, other options (e.g. intravenous iron, erythropoiesis-stimulating agents) should be favoured whenever possible[16], whereas RBC transfusions should be applied in urgent and life-threatening situations only[126].

5. CONCLUSION

IDA is the most common systemic complication and extraintestinal manifestation of IBD, the two most frequent aetiologies being IDA and ACI. However, IBD-associated anaemia is most commonly a prime example of combined IDA and ACI.

The definition of iron deficiency in the presence of inflammation, and consequently its diagnosis, remains challenging, since no gold standard marker has so far been identified, and common biochemical values are an inadequate basis for assessment of iron status in patients who have an inflammatory condition such as IBD.

The major goal of iron supplementation for IDA is to increase haemoglobin levels by >2g/dL or to normal values within 4 weeks, and to fully replenish iron stores. Due to the pathophysiological mechanism of iron deficiency in IBD patients, conventional oral iron formulations (e.g., iron sulphate) are of limited therapeutic value, if any. Thus, intravenous iron supplementation should be favoured in IBD patients with active disease.

Newer oral iron formulations (e.g. ferric maltose) have been introduced in clinical practice and may replace and/or complement intravenous iron formulations in mild or moderate ID, providing efficacy and a more convenient administration route. Whether the same applies in active disease, however, remains to be demonstrated in future clinical trials.

RBC transfusion should only be given when haemoglobin falls below 7g/dL in symptomatic patients and when there is some sort of emergency in correcting anaemia (e.g., haemodynamic instability).

In view of the likelihood of renewed iron deficiency after iron replenishment, periodical monitoring of iron parameters is essential, particularly in patients with active disease.

Expert Opinion

Iron deficiency anaemia is now recognised to be an important complication in IBD patients, with significant repercussions on quality of life and hospitalisation rates. However, weaknesses in its clinical management are still evident, with diagnosis and therapy lacking a standardised approach.

To further improve clinical management of iron deficiency anaemia, better diagnostic tools are needed, both as screening markers for anaemia (e.g. zinc protoporphyrin) and as predictors of sustained therapeutic response (e.g. hepcidin, CHr).

An area of particular interest is the potential treatment of iron deficiency in the absence of anaemia in patients with IBD. Two small studies have shown that intravenous Iron supplementation also has beneficial effects in patients who have iron deficiency without anaemia[127, 128]. Additional clinical trials in IBD patients would be useful to aid decision making. In mild-to-moderate anaemia with normal CRP levels, newer oral iron formulations such as ferric maltol could offer an alternative oral option in patients who do not tolerate ferrous iron. Figure 4 summarises the management of IDA in patients with IBD. Whether oral iron supplementation should be continued only in patients showing a haemoglobin increase ≥1g/dL after two weeks must be clarified in prospective clinical trials. In moderate (haemoglobin <10g/dL) or severe IDA, intravenous iron is the treatment of choice. While the introduction of a new class of highly effective and safe intravenous iron formulations has substantially improved the repertoire of therapeutic options, there are still open issues concerning the prevention of relapsing IDA, which should be the focus of future trials. In particular, studies are needed to address the long-term safety of high doses of intravenous iron and the utility of remission therapy to ensure and sustain normal haemoglobin and ferritin levels and maintain patient quality of life.

It is important to note that iron deficiency frequently recurs after iron replenishment. Consequently, patients require periodical monitoring to assess whether retreatment is

required. Unfortunately, there is still a lack of solid data on when to stop iron supplementation to avoid iron overloading. Thus, well-designed, prospective randomised controlled trials are needed to verify the long-term effects of iron supplementation, as some concerns exist regarding the generation of reactive oxygen species, patient susceptibility to infections, and the potential impact of long-term treatment.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Tables

Table 1: Laboratory findings for the evaluation of anaemia in IBD [modified with permission from[129, 130]]

Table 2: Characteristics of Oral Ferrous Salts versus Intravenous Iron Therapy [mod. from[131]]

Table 3: Characteristics of the different oral iron formulations

Table 4: Characteristics of the different intravenous iron formulations [mod. from[84]]

Table 5: Simplified scheme for the estimation of total iron requirements [modified with permission from[86]]

Table 6: Treatment options to manage HSRs to intravenous iron [modified with permission from both [100, 101] (obtained from the Haematologica Journal website http://www.haematologica.org)]

Figure legends:

Fig. 1: Reticulocyte-based diagnosis of IBD-related anaemia: Anaemia can be extensively classified by combining reticulocytes, reticulocyte production index (RPI) and MCV: Low or normal reticulocyte levels indicate inability to respond adequately to anaemia, either because of inappropriate erythropoiesis caused by micronutrient deficiencies or due to primary bone marrow disease (a; hyporegenerative anaemia), whereas increased reticulocytes denote increased erythropoiesis e.g. due to bleeding or haemolysis), thereby excluding micronutrient deficiencies (b; hyperregenerative anaemia) [adapted from[76]].

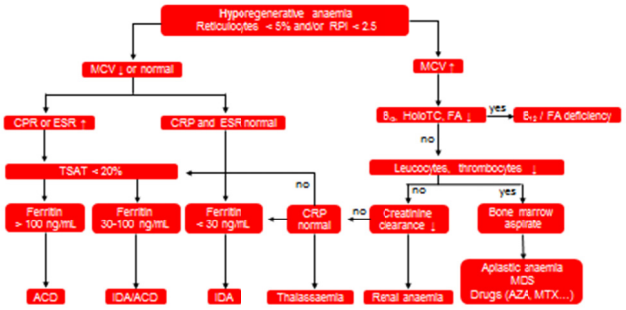

Fig. 1a

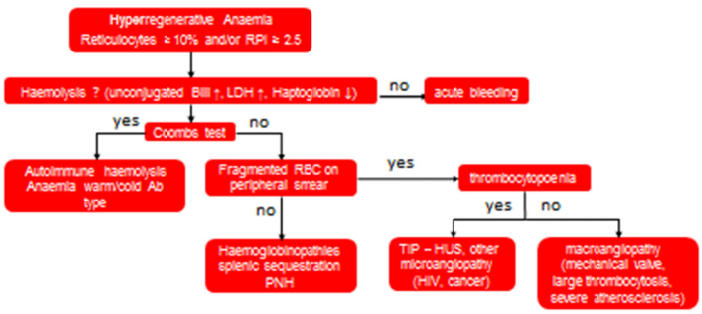

Fig. 1b

Fig. 2: Schematic sequence illustrating the difference of intestinal absorption in ferrous and ferric iron preparations with special emphasis on the generation of non transferrin bound iron [adapted from[63]]

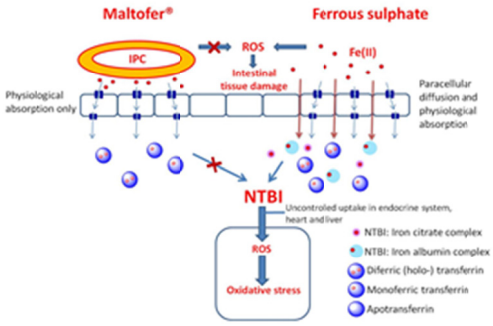

Fig. 2

Fig. 3: Schematic sequence illustrating the metabolism of intravenous iron-carbohydrate complexes (ICC): ICC are taken up into macrophages by endocytosis, leading to endolysosomal degradation of the carbohydrate shell and the released Fe^{3+} is reduced to liberate Fe^{2+}. Subsequently, DMT-1 activity causes extrusion of Fe^{2+} from the endolysosomes to the cytosolic labile iron pool. Finally, iron is extrused from the cytosol to the plasma by FPN and transported by transferrin to the liver, bone marrow and other tissues, or stored as ferritin. Iron from the labile iron pool may also be delivered to the mitochondria, probably via cytosolic iron chaperones [adapted from[82]]. DMT1, divalent metal transporter 1; FP, ferroportin

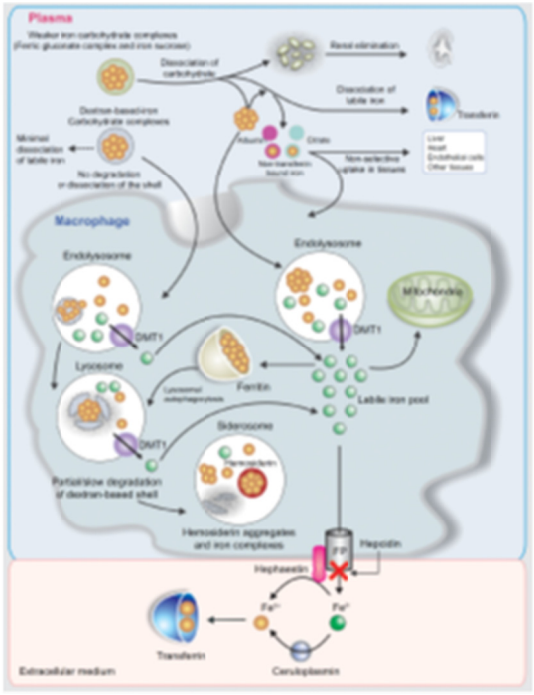

Fig. 3

Fig. 4: Workup for the management of iron deficiency anaemia in patients with IBD [adapted from[76]]

Fig. 4

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Table 1: Laboratory findings for the evaluation of anaemia in IBD (mod. from [129, 130])

Parameter	Reference values*	Interpretation	Comment
MCV and MCH	MCV: 75–90 fl MCH: 27–33 pg per cell	Low levels can indicate concomitant true iron deficiency in ACD. Normal values do not exclude ID as up to 40% of 'pure' IDA cases are normocytic (e.g. in patients treated with AZA or 6-MP)	May be useful to guide iron repletion therapy; in some studies, less sensitive than TfR/ferritin ratio to indicate IDA
Ferritin	♀ 10–250 ng/mL ♂ 18–360 ng/mL	Low (<30 ng/mL): indicative of true iron deficiency even in the setting of inflammation. Normal/high (>100 ng/mL): inadequate iron stores in the setting of inflammation (CRP >5)	Ferritin expression is influenced by inflammation. True iron deficiency can also be present with higher ferritin levels (30 – 100 ng/mL)
Transferrin saturation (TSAT)	20–45%	Low: in ACD and ACD/IDA. High: acute or chronic iron overload (haemolysis, haemochromatosis)	Diurnal variation based on changes in serum iron concentrations. May be helpful for diagnosis of functional ID in the presence of high ferritin levels
Soluble transferrin receptor (sTfR)	0.8–3.3 mg/L*	High expression levels indicate iron requirements for erythropoiesis in the absence of inflammation	Sensitive to iron requirements for erythropoiesis, but expression is also suppressed by inflammation
Transferrin/ferritin ratio **(TfR/F ratio)**	N/A	>2: indicative of true iron deficiency in ACD <1: suggests functional iron deficiency	Better differentiation between ACD and ACD/IDA than sTfR alone. However, some overlap exits
Reticulocyte haemoglobin content (CHr)	28–35 pg	Reduced in ACD/IDA as compared with ACD; indicator for ongoing erythropoiesis and iron availability for reticulocytes	Determination dependent on specific technical equipment Overlap between ACD and ACD/IDA reduces

			discriminative potential
Hypochromic red blood cells (%HYPO)	< 5(6)%	Higher percentage in true iron deficiency; indicator for iron availability for erythropoiesis	Determination dependent on specific technical equipment Sensitivity for IDA in comparison to other methods unclear
Zinc protoporphyrin (ZPP)	< 40 µmol/mol Hb	40–80 µmol/mol Hb: ID without anaemia > 80 µmol/mol Hb: IDA	Should be interpreted cautiously in the setting of zinc deficiency. Not suitable to guide iron repletion therapy
Hepcidin	N/A	High levels in ACD Normal or reduced concentrations in ACD/IDA	Hepcidin levels seem to be more stringently controlled by iron requirements for erythropoiesis than by inflammation; assays not yet widely available
Haptoglobin (HPT)	300–2,000 mg/L	Reduced levels are indicative of haemolysis Increased levels may also be found in association with inflammation	Identification of haemolytic anaemia
Folic acid	2.0–9.0 ng/mL (4.5–20.4 nmol/L)	Decreases over time with ongoing erythropoiesis or gastric inflammation, or in association with treatment (e.g. methotrexate)	
Vitamin B_{12}	200–900 pg/mL (~147–645 pmol/L)	For clinical deficiency, sensitivity 95%–97% and specificity ≤ 80% For isolated biochemical deficiency, insufficient sensitivity and specificity (see Table 4)	Should be part of initial and follow-up evaluation of anaemic patients with CD and ileoanal pouch
Vitamin D	25 OH vitamin D > 20 ng/mL:	< 20 ng/mL: deficiency 20-30 ng/mL: insufficiency > 30 ng/mL: sufficiency	1,25 OH vitamin D may be helpful for interpretation of HPT in the presence of normal calcium and 25 OH vitamin D levels

ACD, Anaemia of chronic disease; AZA; azathioprine; CD, Crohn's disease; CRP, C-reactive protein; Hb, haemoglobin; HPT, haptoglobin; ID, iron deficiency; IDA, iron deficiency anaemia; MCH, mean corpuscular haemoglobin; MCV, mean corpuscular volume; 6-MP, 6-mercaptopurine;

Table 2: Characteristics of oral ferrous salts versus intravenous iron therapy [mod. from [131]]

Characteristic	Oral Iron	Intravenous Iron
Intestinal absorption	• Limited daily intestinal absorption results in slower Hb increase • ineffective repletion of iron stores • Uptake is impaired in the setting of disease (e.g. coeliac disease, • anaemia of chronic disease, autoimmune gastritis) • Impaired by concomitant food (depending on formulation) • Impaired by concomitant medication (e.g. phosphate binders, gastrointestinal medications that reduce acidity)	• Parenteral administration • Effective even in presence of inflammation
Safety	• Gastrointestinal adverse events affect a high proportion e.g. constipation, dyspepsia, bloating, nausea, diarrhoea, heartburn • Most frequent with ferrous sulphate	• Good safety profile, risk of (rare) anaphylaxis with dextran-containing formulations Risk of (rare) hypersensitivity reactions • Side effects at injection site may occur
Oxidative stress	• Mucosal injury and/or potential exacerbation of disease activity may occur in inflammatory bowel disease. • Alteration of microbiota	• Less stable preparations (e.g. sodium ferric gluconate, iron sucrose similars) when given in high doses can induce oxidative stress by releasing some more "weakly bound" iron, than stable (robust) iron complexes (e.g. ferric carboxymaltose, iron isomaltoside)
Adherence	• Pill burden: usually 3 tablets per day • Dose-dependent gastrointestinal side effects (nausea, vomiting, abdominal pain, constipation) limits patient adherence.	• Requires health care professional and facilities for cardiopulmonary resuscitation
Convenience	• Available over the counter • Administered at home	• Requires administration by a health care professional, with associated increased costs
Costs	• Inexpensive	• More expensive per dose but fewer doses required

Table 3: Characteristics of the different oral iron formulations

Formulation	Ferrous bisglycinate	Ferrous fumarate	Ferrous gluconate	Ferrous sulphate	Ferric ammonium citrate	Ferric maltol (ST 10)*	Polysaccharide–iron complex	Ferric pyrophosphate (sucrosomial iron)
Brand name	Bluebonnet Chelated Iron Albion, Amino Acid Chelate Ferrocehl etc.	Ferro-Sequels time release tablets, Nephro-Fer, Feretts, Reliva, etc.	Fergon, Floradix, etc.	Ferro sanol, FeroSul, Fer-in-Sol, Fer-Gen-Sol, etc.	Iron Citrate	Feraccru	FeraHeme	Sideral® Forte
Available dosage forms	Capsules, tablets	Tablets, chewable tablets	Tablets	Oral solution, tablets, EC tablets, film-coated tablets	Capsules	Capsules	Capsules, solution, film-coated tablets	Oral solution, tablets
Elemental iron (mg) per Capsule	27	50–150	27–38	65	25	30	100	30
% Elemental Iron	20	33	12	20	18		100	
Additional information	May be less likely to cause GI intolerance	Efficacy/tolerability similar to ferrous sulphate Almost tasteless	Efficacy/tolerability similar to ferrous sulphate	Formulation of choice for treatment of iron-deficiency anaemia given its general tolerability, effectiveness, and low cost.	Less bioavailable than ferrous salts	Shown to cause less GI irritation	Promoted to cause less GI irritation (unproven)	Promoted to cause less GI irritation (unproven)

GI, gastrointestinal; EC, enteric-coated.

Table 4: Characteristics of the different intravenous iron formulations (adapted from [84])

Formulation	Sodium ferric gluconate in sucrose solution*	Iron sucrose‡	LMWID‡	Ferric carboxymaltose	Iron isomaltoside 1000	Ferumoxytol
Brand name	Ferrlecit	Venofer	Cosmofer INFeD	Ferinject Injectafer**	Monofer	FeraHeme
Manufacturer	Sanofi-Aventis	Vifor	Pharmacosmos	Vifor	Pharmacosmos	AMAG
Molecular weight, Da	37 500* 200 000† 164 100‡	43 300* 252 000† 140 100‡	103 000* 410 000† 165 000‡	150 000* not measured† 233 100‡	69 000* not measured† 150 000‡	185 000* 731 000† 275 700‡
Reactivity	High	Moderate	Low	Low	Low	Low
Half life, h	1.42	5.3	27 to 30	7.4/9.4¶	23.2	14.7
Area under the curve, mg Fe/L × h§	35.0	83.3	1371	333/6277¶	1010	922
Clearance, L/h	2.99	1.23	……	0.26/0.16¶	0.10	0.11
Maximum Single Dose of *Infusion*	125mg iron (or 62.5mg iron in some markets)	100mg to 400mg iron (500mg iron in some markets)	20mg Fe/kg 20mg Fe/kg (drip infusion)	Up to 1000mg iron in a single dose** (maximum 20mg Fe/kg), or 200mg in haemodialysis patients	20 mg Fe/kg 200mg to 1000mg Fe/Week (drip infusion)	N/A
Maximum Single Dose of *Injection*	125mg iron	100mg to 200mg iron	20mg Fe/kg	Up to 1000mg iron in a single dose** (maximum 15 mg Fe/kg)	100mg to 200mg iron up to 3 times a week	510mg iron followed by a second 510mg iron injection 3 to 8 days later
Minimum Duration of *Infusion*	1 h	100mg, 15 min 200mg, 30 min 300mg iron, 1.5 to 2.5 h 400mg iron, 2.5 h 500mg iron, 3.5 h	Total dose: 4 to 6 h Drip infusion: 15 min for first 25mg iron, wait 15 minutes, administer remainder at minimum 20 min/dL solution	100mg to 200mg iron, no minimum ≥200 mg to 500mg iron, 6 min ≥500 mg to 1000mg iron, 15 min	Total dose: 0mg to 10mg Fe/kg, 30 min 11mg to 20mg Fe/kg, 60 min Drip infusion: 0 to 5mg Fe/kg, 15 min 6 to 10mg Fe/kg, 30 min	N/A

					11 to 20mg Fe/kg, 60 min	
Minimum Duration of *Injection*	12.5mg Fe/min	5 to 10 min	Administer 25mg Fe over 1 to 2 min, wait 15 min, administer remainder	100mg to 200mg iron, no minimum ≥ 200mg to 500mg iron, 100mg Fe/ min ≥ 500mg to 1000 mg iron, 15 min	50mg Fe/min	17 s (30mg Fe/s)
Test Dose Required	No	Yes/No#	Yes	No	No	No
Postdose Observation required	Yes (minimum 30 min)	Only in some markets (e.g. USA, minimum 30 min)	Only in some markets (e.g. USA, minimum 30 min)	No	No	Yes (minimum 30 min)

ADE: Adverse drug event; HMWID: High-molecular-weight iron dextran; LMWID: Low-molecular-weight iron dextran; TDI: Total dose infusion.

*Method based on the USP Iron sucrose injection, relative to a pullulan standard

†Method according to Balakrishnan and colleagues, relative to a protein standard

‡Method according to Jahn and colleagues, relative to dextran standards

§Standardised for a dose of 100mg iron

¶For Ferinject®, the second PK-values represent the results from the clinical study with a dose of 1000mg iron.

#Varies between markets

**Injectafer® in some markets. See Ferinject® prescribing information for dosing limitations.

Table 5: Simplified scheme for estimation of total iron requirements [adapted from [86]]

Degree of iron deficiency	Haemoglobin level (g/dL)	Dose (mg)	
		Body Weight <70 kg,	Body Weight ≥70 kg
No anaemia	Normal	500	1000
Moderate	10-12 (women) 10-13 (men)	1000	1500
Severe	7-10	1500	2000
Critical	<7	2000	2500

Table 6: Treatment options to manage HSRs to intravenous iron (mod. from [100, 101])

Severity	Symptoms	Treatment options
Mild HSRs	Itching, urticaria, flushing, sensation of heat, slight chest tightness, hypertension and back/joint pains	Stop infusion temporarily and watch symptoms and signs. If symptoms improve the infusion can be restarted cautiously
Moderate HSRs	As in mild reaction + cough, chest tightness, nausea, shortness of breath, tachycardia and hypotension	Stop infusion and consider IV fluids and IV corticosteroids
Severe HSRs **= life-threatening anaphylaxis**	As in moderate + sudden onset and rapid aggravation of symptoms + wheezing, stridor, periorbital oedema, cyanosis, loss of consciousness and cardiac/respiratory arrest	As for moderate HSRs + IM or IV adrenaline (epinephrine) + consider β_2-adrenoceptor agonist inhaler, O_2 by facemask, act according to local standard anaphylaxis guidelines