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EDUCATIONAL SERIES

Managing Iron Deficiency and Iron Deficiency Anaemia in IBD

About the Reviewer

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Abbreviations used in this review

ACD = anaemia of chronic disease
CD = Crohn's disease
CRP = C-reactive protein
ECCO = European Crohn's and Colitis Organisation
IBD = inflammatory bowel disease
IDA = iron deficiency anaemia
IV = intravenous
RCT = randomised controlled trial
UC = ulcerative colitis
WHO = World Health Organization

About this review

This review is intended as an educational resource for health professionals. It discusses the diagnosis and treatment options available in New Zealand for iron deficiency and iron deficiency anaemia (IDA) associated with inflammatory bowel disease (IBD) in both the primary and secondary healthcare settings. An up-to-date review of this condition with guidelines and recommendations is presented. Summaries of reviews supporting the recommendations are included, along with expert commentary.

Introduction

Iron deficiency is one of the most common and potentially treatable health problems worldwide.[1] The 2008/9 New Zealand Nutrition survey revealed an overall prevalence of iron deficiency of 4.2%, and of IDA of 2%, with rates as high as 12.1% and 6%, respectively, for females aged 31-50 years.[2] Conditions associated with chronic blood loss and/or chronic inflammation, such as IBD, increase the risk of developing IDA.[3] In severe cases, anaemia can lead to the requirement for blood transfusions.

Estimates suggest that approximately 60-80% of individuals with IBD experience iron deficiency, with an estimated one-third developing recurrent anaemia.[4] Alarmingly, the prevalence seems to be even higher in children with IBD, with rates of iron deficiency reported as high as 90-95% and anaemia of 75%.[5] With an estimated 15,000 individuals in NZ affected by IBD, the number of patients suffering from this complication is likely to be significant.[6]

IDA is a leading cause of morbidity and hospitalisation in patients with IBD and both iron deficiency and IDA have substantial impacts on quality of life.[3] Surprisingly, while IDA is one of the most common extraintestinal complications of IBD, it often goes undiagnosed and untreated.[7]

Chronic fatigue, a common symptom of anaemia, may debilitate IBD sufferers as much as abdominal pain and diarrhoea.[8] Other symptoms of iron deficiency including impaired physical performance, impaired cognitive function, headache, tachycardia, dizziness, exertional or resting dyspnoea, loss of libido, sleeping disorders, poor skin, hair and nail growth, pica, paraesthesia, restless legs syndrome, impaired thermoregulation and impaired immune function also have considerable quality of life and socioeconomic impacts.[4,9]

Iron deficiency *per se* is not a diagnosis and it is imperative to identify the cause of the deficiency. In the setting of IBD, an adequate understanding and diagnosis of the underlying cause of anaemia and special considerations for its treatment are critical.[4] Given the significant impact of anaemia and its high prevalence in this population, regular screening for anaemia and iron deficiency is important. Prompt and effective iron supplementation is essential to minimise the impact of this complication and clinical evidence shows that simple measures to address iron deficiency can lead to improved outcomes in this patient group.[4,8-12] There is strong evidence that treatment of iron deficiency without anaemia can improve fatigue, exercise performance, muscle function, verbal learning and memory, and quality of life.[3,8] Also, a proactive approach to anaemia management, rather than waiting for anaemia recurrence, has been shown to be cost-effective, with US estimates of cost associated with the care of anaemic IBD patients being more than twice that of non-anaemic patients.[3] Furthermore, the cost of blood transfusions far exceeds that of IV iron infusion and should be avoided from both a health and safety and economic view point.

Understanding iron status

Iron status can be thought of as a continuum from iron deficiency with anaemia, to iron deficiency in the absence of anaemia, to normal iron levels with variable amounts of stored iron, to iron overload.[1] Iron deficiency develops as a result of a long-term negative iron balance and can result from a poor diet or disease.[1] In iron deficiency, normal iron stores (in the form of haemosiderin and ferritin) are diminished and the supply of iron to the transport protein apotransferrin is compromised, resulting in an increase in transferrin receptors in the circulation and on the surface of cells (including the circulating erythrocytes). Iron is essential for optimal functioning of all cells of the body. When iron-deficient erythropoiesis occurs, haemoglobin concentrations are reduced to suboptimal levels. The lack of mobilisable iron stores results in a detectable change in laboratory parameters including haemoglobin concentration, transferrin saturation, serum ferritin levels, mean corpuscular haemoglobin concentration, mean corpuscular volume and total iron-binding capacity.

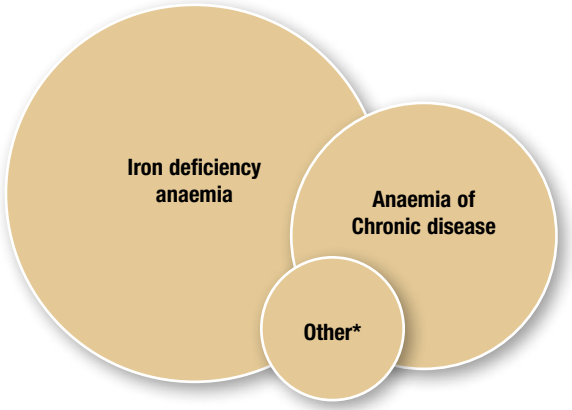
Anaemia in IBD

While iron deficiency is the predominant cause of anaemia in IBD, the etiology of anaemia in this disease may be multifactorial resulting from a combination of IDA, anaemia of chronic disease (ACD) and other causes including drugs (e.g. sulfasalazine and thiopurines), vitamin B_{12}/folic acid deficiency, haemolysis, myelodysplastic syndrome, aplasia and haemoglobinopathies (see **Figure 1**).[4,7-14] With the less common causes of anaemia, specific non-iron approaches may be appropriate such as changing medications, vitamin B_{12} and folic acid supplementation, and treatment with erythropoietin.[15]

Iron deficiency in IBD is usually a result of dietary restrictions, malabsorption of iron in the small intestine and/or intestinal bleeding.[16] IDA, a type of microcytic anaemia, results when iron stores are exhausted and the supply of iron

to the bone marrow (the site of erythropoiesis) is compromised.[15] Indicating a severe state of iron deficiency, IDA results when haemoglobin concentrations fall below the lower limit of normal.

ACD, also a type of microcytic anaemia, is due to the influence of inflammatory mediators on iron metabolism, erythropoiesis and erythrocyte survival.[8] ACD occurs with inflammation, infection and malignancy. The anti-microbial peptide hepcidin plays a pivotal role in this and is upregulated in diseases such as IBD, restricting iron absorption in the duodenum and trapping iron within macrophages and hepatocytes.[4,17] The result is a functional iron deficiency, a situation with normal or elevated iron stores and reduced erythropoiesis.[15] Treatment of IBD in patients with ACD should be optimised with anaemia-specific treatments.[15] Depending on the underlying condition and in certain cases, individuals with ACD may be treated with blood transfusion, erythropoiesis-stimulating agents and iron supplementation.[18]



*resulting from agents used to treat IBD, vitamin B_{12}/folic acid deficiency, haemolysis, myelodysplastic syndrome, aplasia or haemoglobinopathies

Figure 1. Etiology of anaemia in IBD.[14]

Testing for iron deficiency and anaemia

The 2015 ECCO guidelines on the management of iron deficiency and anaemia in IBD recommend that all patients with IBD be regularly assessed for anaemia.[15] The guidelines recommend laboratory screening for full blood count (including reticulocytes), serum ferritin, transferrin saturation, and C-reactive protein (CRP) every 6-12 months for those in remission or with mild disease, and at least every 3 months for those with active disease. The guidelines also recommend that serum levels of vitamin B_{12} and folic acid be measured at least annually.

Iron deficiency (without anaemia)

Iron deficiency doesn't always develop into anaemia and sometimes iron deficiency is the only sign of disease activity in IBD patients.[15,18] Iron deficiency is reported to be 3-fold more common than IDA.[18] Normal haemoglobin concentrations do not exclude iron deficiency, as normal body iron stores must be significantly depleted before haemoglobin levels fall to those indicative of anaemia.[19,20] Also, while a normal complete blood count is evidence that the iron supply is adequate, it does not indicate that iron stores are present, nor does serum iron level accurately reflect stored iron. In contrast, serum ferritin concentrations do reflect iron stores and are therefore considered the best test to verify iron deficiency.[1,15,21] However, it must be kept in mind that ferritin concentrations increase with chronic inflammation such as in IBD and may be high despite empty iron stores – for this reason, cut off levels specific for IBD have been developed.[15,16] In the absence of clinical, endoscopic or biochemical evidence of active IBD, iron deficiency is likely if the serum ferritin concentration is <30 µg/L, while in the presence of active disease this cut off is increased to 100 µg/L (see **Table 1**).

Table 1. Degree of iron deficiency evaluated by serum ferritin in adults with IBD[15,16]

	Serum Ferritin (µg/L)
Depleted iron stores in healthy adults or patients with quiescent IBD	<30
Depleted iron stores during active IBD	<100
Adequate iron stores	>100
Potential iron overload	>800

Anaemia

Anaemia is defined as a haemoglobin concentration below that considered normal. The WHO criteria for normal haemoglobin levels are shown in **Table 2,** along with cut-off concentrations for mild, moderate and severe anaemia.[21] It should be noted that even in mild anaemia, iron deficiency is already advanced and that iron deficiency has consequences even when no anaemia is clinically apparent.[21] Furthermore, normal haemoglobin levels vary with altitude, ethnicity and smoking status.[15,21]

Table 2. Haemoglobin levels to diagnose anaemia at sea level (g/dL) – WHO classification[21]

	Non-anaemia*	Anaemia*		
Age or gender group		**Mild**	**Moderate**	**Severe**
Children 6 months to 4.9 years	>11.0	10.0-10.9	7.0-9.9	<7.0
Children 5-11 years	>11.5	11.0-11.4	8.0-10.9	<8.0
Children 12-14 years	>12.0	11.0-11.9	8.0-10.9	<8.0
Non-pregnant women (>15 years)	>12.0	11.0-11.9	8.0-10.9	<8.0
Pregnant women	>11.0	10.0-10.9	7.0-9.9	<7.0
Men (>15 years)	13.0	11.0-12.9	8.0-10.9	<8.0

*Haemoglobin in g/dL

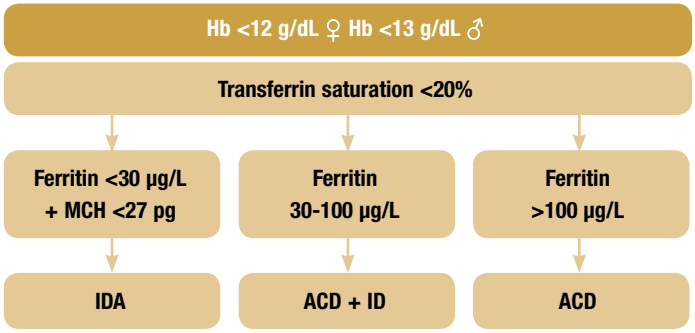
Differential diagnosis of anaemia – IDA vs ACD

When anaemia is present, the next step is to determine its etiology. While there is no single test for determining this, haemoglobin, CRP, serum ferritin, transferrin saturation and mean corpuscular haemoglobin concentrations are routinely used to differentiate between IDA and ACD (see **Table 3 and Figure 2**).

Table 3. Laboratory findings in anaemia in IBD[14,19]

Laboratory measures	IDA	ACD	IDA and ACD
Haemoglobin	Reduced	Reduced	Reduced
CRP	Normal	Increased	Increased
Serum ferritin	Reduced	Increased	Increased or normal
Transferrin saturation	Reduced	Reduced	Reduced

ACD = anaemia of chronic disease; CRP = C-reactive protein; IDA = iron deficiency anaemia



ACD = anaemia of chronic disease; ID = iron deficiency; IDA = iron deficiency anaemia; MCH = mean corpuscular haemoglobin

Figure 2. Algorithm for the diagnosis of IDA and ACD in IBD.[19]

Estimating iron requirements

A simple reliable estimate of iron requirement in IDA for use in clinical practice is based on baseline haemoglobin level and body weight (see **Table 4**).[15,22] This scheme, recommend by ECCO has proven useful in the treatment of IBD patients with IDA.[15] In iron deficiency without anaemia, a minimum of 500-1000 mg should be considered.[15] Alternatively, Ganzoni's formula can be used.[23]

Table 4. Simple scheme for the estimation of iron need in IDA[15]

Haemoglobin g/dL	Body weight <70 kg	Body weight ≥70 kg
10-12 [women]	1000 mg	1500 mg
10-13 [men]	1000 mg	1500 mg
7-10	1500 mg	2000 mg

NB. Patients with a haemoglobin level <7.0 g/dL likely need an additional 500 mg dose

A useful online calculator for determining iron requirement is available from: http://reference.medscape.com/calculator/iron-replacement-parenteral-dosing

Treatment recommendations

The following treatment options for iron deficiency or IDA should only occur in the setting of treating bleeding, active disease and exclusion of primary haematological problems. **Figure 3** shows a useful algorithm for the management of IDA in IBD.

Treating iron deficiency and preventing IDA

Iron deficiency without anaemia can cause symptoms and affect quality of life.[15] The goal of iron supplementation in this scenario is to normalise haemoglobin levels and iron stores.[15] The ECCO guidelines state that the decision to supplement iron in those who are iron deficient but not anaemic should be based on the patient's history, symptoms and individual preferences.[15] NZ Best Practice Guidelines suggest that, in general, iron supplementation should be considered for symptomatic patients (those with fatigue etc.) and those at higher risk of iron depletion progressing to anaemia.[18] In the absence of inflammation or ongoing blood loss, oral iron should be satisfactory to rapidly replenish iron stores and treatment for 3 months is generally appropriate for most patients.[18]

Treating IDA

Quality of life improves significantly with correction of anaemia and in IBD this improvement appears to be independent of disease status.[22,24] The 2015 ECCO guidelines recommend iron supplementation in all IBD patients with IDA.[15] Recurrence of iron deficiency is lower in patients with higher post-treatment ferritin concentrations. Studies have shown that post-treatment serum ferritin concentrations >400 µg/L prevent recurrence of iron deficiency within 1-5 years better than concentrations below this value. In the event of recurrence after successful treatment of IDA, retreatment with IV iron should be considered as soon as ferritin concentrations drop below 100 µg/L (see **Figure 3**).

ECCO Recommendations:[15]

Iron deficiency: The decision to supplement iron in those who are iron deficient but not anaemic should be based on the patient's history, symptoms and individual preferences – the goal of preventive treatment is to maintain serum ferritin and haemoglobin levels within the normal range.

Oral iron supplementation is recommended for patients with mild anaemia (see WHO classification **Table 2**) and clinically inactive IBD with no previous history of iron intolerance.

IV iron supplementation is recommended as first-line treatment in patients with clinically active IBD, with previous intolerance to oral iron, with haemoglobin levels <10 g/dL, and in patients requiring erythropoiesis-stimulating agents.

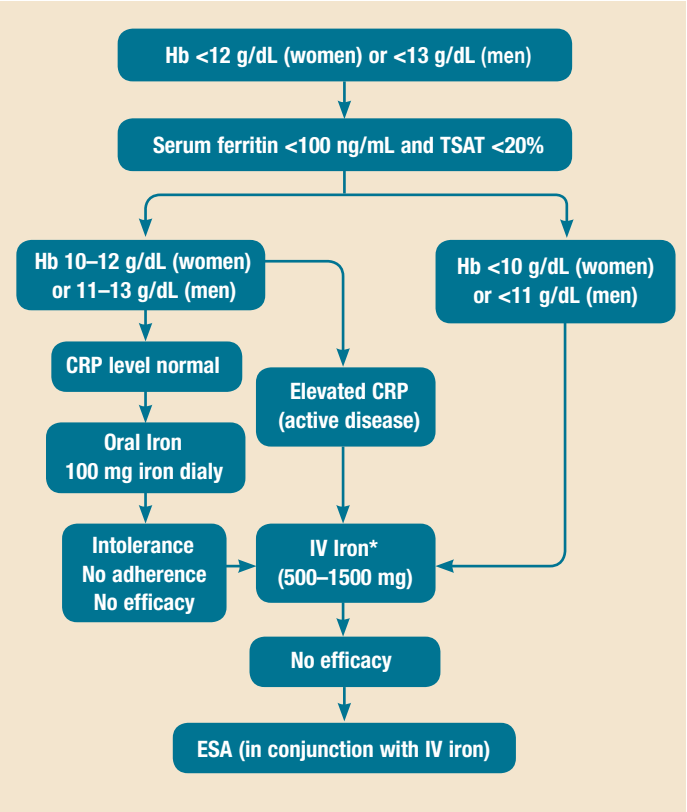
Retreatment with IV iron after successful treatment should be initiated as soon as serum ferritin drops below 100 µg/L or haemoglobin below 12-13 g/dL (according to gender).

Erythropoietin

The ECCO guidelines state that erythropoiesis-stimulating agents (such as epoetin alfa [Eprex®] and epoetin beta [Erythropoietin beta]) may be used in IBD patients with ACD who have had an insufficient response to IV iron despite optimised IBD therapy – the target haemoglobin level should not be higher than 12 g/dL. IV iron can be used concomitantly with erythropoietin.[15] Combination therapy with IV iron and erythropoietin demonstrates a faster and larger haemoglobin increase than IV iron alone.[8] In view of potential adverse cardiovascular events, erythropoiesis-stimulating agents should be restricted to those with a haemoglobin level <10 g/dL who do not adequately respond to IV iron replacement alone over 4 weeks.[4]

Blood transfusions

Blood transfusions are generally restricted to situations where there is risk of cardiovascular instability due to severe anaemia, or when symptomatic anaemia persists despite iron treatment.[18] The ECCO guidelines state that red blood cell transfusion may be considered for the treatment of anaemia when haemoglobin concentration is below 7 g/dL, or above if symptoms or particular risk factors are present.[15] Blood transfusions should be followed by IV iron supplementation.[15]



CRP = C-reactive protein; ESA = erythrocyte stimulating agent; Hb = haemoglobin; IV = intravenous; TSAT = transferrin saturation

*Ferric carboxymaltose is the preferred IV agent for its low side effect profile and relative ease of administration – in NZ ferric carboxymaltose is used predominantly in the outpatient setting, while polymaltose is the agent predominantly used in inpatients.

Figure 3. Algorithm for the management of IDA in IBD.[4]

Iron supplements available in NZ

A variety of different salt forms of iron are available in NZ (see **Table 5**).[25] There appears to be no particular advantage of one ferrous salt type over another, provided adequate iron is administered, and choice is dependent upon the risk of sides effects, cost and convenience. Much of the success of iron supplementation depends on the effectiveness of the delivery system.[1]

There are clear advantages of using IV iron over oral iron in certain patients such as those with active IBD or intolerance to oral iron. Iron infusions are usually carried out in secondary care, although some general practices are now offering this therapy.[18] Patients undergoing iron infusion must be closely monitored during the infusion and resuscitation equipment and anaphylaxis treatment be readily available.

Table 5. Iron supplements available in New Zealand for the treatment of iron deficiency and IDA[25]

Iron salt	Trade name	Additional ingredient	Route	Dose/Formulation	Elemental iron
Ferrous fumarate	Ferro-Tab		Oral	200 mg tablet	65 mg
	Ferro-F-Tab	Folic acid 350 µg	Oral	310 mg tablet	100 mg
Ferrous sulphate	Ferrograd		Oral	325 mg long-acting tablet	105 mg
	Ferodan		Oral	150 mg/5 mL liquid	30 mg/5 mL
	Ferrograd F	Folic acid 350 µg	Oral	325 mg tablet	105 mg
	Ferrograd C	Ascorbate sodium 562.4 mg	Oral	325 mg tablet	105 mg
Ferric carboxymaltose	Ferinject®		IV	100 mg/2 mL 500 mg/10 mL	50 mg/ mL
Iron polymaltose	Ferrum H®		IM/IV*	100 mg/2 mL	50 mg/ mL
Iron sucrose	Venofer®		IV	100 mg/5 mL	20 mg/ mL

*Ferrum H® when used IV is off label

Monitoring response

Generally, the lower the baseline haemoglobin concentration, the longer it takes for haemoglobin concentrations to normalise after treatment.[15] An acceptable speed of response is considered to be an increase in haemoglobin of ≥2 g/dL within 4 weeks of treatment.[15] While the risk of iron overload in patients with chronic bleeding is low, therapy should be guided by the following upper limits: serum ferritin >800 µg/L; transferrin saturation >50%. Once haemoglobin has normalised, treatments should be continued for another 3 months in order to replenish iron stores.[25] Current recommendations are that IBD patients be monitored (haemoglobin, ferritin, transferrin saturation and CRP) for recurrent iron deficiency every 3 months for at least a year after correction, and then every 6 to 12 months.[15]

Evidence suggests that even those with quiescent disease and replenished iron stores via supplementation have difficulty maintaining a positive iron balance and are at risk of developing recurring anaemia.[3] Evidence also suggests that IDA recurs in 26.7% of patients treated with IV iron (ferric carboxymaltose).[3] Recurrent IDA in IBD may be indicative of persistent intestinal activity even if there is clinical remission and inflammatory parameters such as CRP are normal.[15]

Oral versus parenteral iron therapy

Usually the initial approach for treating IDA in the general population is with oral iron (ferrous fumarate or ferrous sulphate) and some comparative studies have shown that this route is as effective as IV iron in improving haemoglobin levels, however, in the IBD population IV iron has been shown to replenish iron stores more quickly and effectively, and to improve quality of life to a greater extent than oral supplementation.[15,26-28] Among clinical studies and meta-analyses, there is compelling evidence that IV iron is better tolerated than oral iron in patients with IBD and there is a tendency to favour parenteral iron supplementation over oral iron in this patient group because many experience severe intolerance to oral preparations.[3,10,29] The reported incidence of discontinuation of oral iron therapy in patients with Crohn's disease was reported to be up to 21% in a systematic review of eight studies, with nausea, abdominal pain and diarrhoea being the main reported symptoms of intolerance.[13]

Oral iron supplementation has specific limitations in patients with IBD with active disease, with reduced iron absorption through the gastrointestinal tract.[8] In this patient group, oral iron supplementation has been associated with oxidative stress at the site of bowel inflammation.[8] There is also evidence that oral iron interferes with microbial diversity in the gut in IBD.[30]

A promising new oral agent, ferric maltol, administered at a dose of 30 mg twice daily for 52 weeks, has been assessed in a Phase 3 study and has shown efficacy and tolerability in patients with IDA and mild-to-moderate IBD.[31]

In IBD, the general consensus is that IV iron should be used when a quick response is needed and IV iron is recommended as first-line treatment in patients with clinically active IBD, with previous intolerance to oral iron, with haemoglobin levels <10 g/dL, and in patients requiring erythropoiesis-stimulating agents.[15] Parenteral iron supplementation is shown to be effective for both the reversal of anaemia and maintenance of iron stores.[15]

A comparison of parenteral iron formulations

In choosing a parenteral (IV or IM) formulation for iron supplementation, convenience of administration is a major factor.[32] Iron sucrose [Venofer®] is typically administered in New Zealand as a 2-3 hour infusion at a maximum of 200 mg per injection, sometimes requiring multiple outpatient visits and repeated IV access to deliver required doses.[33] IM or IV (off label) iron polymaltose [Ferrum H®] is limited to 200 mg/day.[34]

Ferric carboxymaltose [Ferinject®] has advantages in that it is able to be infused rapidly, allows for a large replenishment dose of up to 1000 mg of iron in a single 15 minute infusion and does not require a test dose to be administered.[32,35] Ferric carboxymaltose has significant benefit for use in the outpatient or community setting, is cost-effective, and has proven efficacy and safety.[10,32] Ferric carboxymaltose is thus the preferred IV agent for iron replacement in the outpatient setting. In New Zealand, ferric carboxymaltose has been on the Hospital Medicines List for use in DHB hospitals since 2014.[36] Ferric carboxymaltose is indicated for the treatment of iron deficiency in adults and children >14 years of age when oral iron preparations are ineffective or cannot be used.[35]

IV iron formulations should not be used in the first trimester of pregnancy and should only be administered in the second and third trimester of pregnancy if the benefits of treatment outweigh the potential risk to the fetus.[33-35]

EXPERT COMMENTARY ON KEY STUDIES OF ORAL AND PARENTERAL IRON REPLACEMENT IN IBD

Iron treatment and inflammatory bowel disease: what happens in real practice?[37]

Authors: Lugg S et al.

Summary: This questionnaire-based audit of anaemia treatment was conducted in 87 adult IBD (60 CD, 25 UC, 2 microscopic colitis) hospital outpatients to determine the form and frequency of iron prescribed, treatment duration, adverse events and completion rate. In total, 85 patients received iron tablets and 15 patients also received IV iron. Adverse events were reported by 43 (51%) patients, with no clear relationship to dosage, and 26 (32%) patients failed to complete treatment. With oral iron, only 36 (42%) patients completed treatment without adverse events, and haemoglobin level normalised in about 30% of these patients; median haemoglobin change 12.5 g/L. Median treatment duration in those without adverse events was 4.5 months; in those with adverse effects the median treatment duration was 2 months. With IV iron only one patient reported an adverse effect.

Comment: In spite of evidence to suggest superiority of IV iron to oral, and concerns regarding side effects of oral therapy in patients with IBD, this study identifies that the majority of patients are still prescribed oral iron therapy at some stage during the course of their disease with a high likelihood of treatment failure. Even amongst those able to complete a course of oral iron, only 36% had a normalisation of haemoglobin. The nature of this study makes it unclear whether iron was prescribed in primary or secondary care. Nevertheless, it highlights the need for close monitoring of patients prescribed oral iron, with a clear plan for escalation to IV therapy in the event of treatment intolerance or failure.

A novel intravenous iron formulation for treatment of anemia in inflammatory bowel disease: the ferric carboxymaltose (FERINJECT) randomized controlled trial[28]

Authors: Kulnigg S et al.

Summary: This randomised controlled trial of IV ferric carboxymaltose (maximum 1000 mg iron weekly infusion intervals until calculated total iron deficit reached) in 200 patients with IBD compared it with oral ferrous sulfate (100 mg twice daily) for 12 weeks. Median haemoglobin increased from 8.7 to 12.3 g/dL with IV ferric carboxymaltose versus an increase from 9.1 to 12.1 g/dL with oral ferrous sulfate, meeting pre-specified non-inferiority criteria. The response (haemoglobin increase >2.0 g/dL) rate was higher with ferric carboxymaltose than with oral ferrous sulfate at 2 ($p = 0.0051$) and 4 weeks ($p = 0.0346$). In the ferric carboxymaltose group, median ferritin rose from 5.0 to 323.5 µg/L at 2 weeks, but declined thereafter to reach 43.5 µg/L at 12 weeks. In oral ferrous sulfate recipients, ferritin rose from 6.5 at baseline to 28.5 µg/L at 12 weeks. Treatment-related adverse events were observed in 28.5% of ferric carboxymaltose and 22.2% of oral ferrous sulfate recipients leading to discontinuation in 1.5% and 7.9% of patients.

Comment: The IV iron preparations polymaltose and sucrose can be cumbersome and time consuming to use and are occasionally associated with severe adverse events. Ferric carboxymaltose is a novel IV preparation, which can deliver high doses of iron with a rapid infusion time (15 min) without safety concerns to date. In this study, ferric carboxymaltose was demonstrated to be non-inferior to oral iron therapy in the form of iron sulphate. The treatment regime was based on the total iron deficit calculated by Ganzoni's formula and achieved a median increase in haemoglobin of 3.7 g/dL at 12 weeks. Tolerance of oral therapy in this cohort was good, which is often not the case in practice, and ultimately ferric carboxymaltose may prove to be a superior option.

FERGIcor, a randomized controlled trial on ferric carboxymaltose for iron deficiency anemia in inflammatory bowel disease[22]

Authors: Evstatiev R et al.

Summary: This randomized, controlled, open-label, multinational study, in 485 patients with IBD and IDA (ferritin <100 µg/L, haemoglobin 7-12 g/dL [female] or 7-13 g/dL [male]) tested a novel fixed-dose ferric carboxymaltose regimen (three infusions of 1000 or 500 mg iron) versus individually Ganzoni-calculated iron sucrose (up to 11 infusions of 200 mg iron). More patients achieved the primary endpoint of haemoglobin response (haemoglobin increase ≥ 2 g/dL) with ferric carboxymaltose than with iron sucrose (65.8% vs 53.6%; $p = 0.004$); the secondary endpoint haemoglobin normalisation (72.8% vs 61.8%; $p = 0.015$) also favoured ferric carboxymaltose. By week 12, quality of life measures were improved with both treatments. Both agents were well tolerated and no new drug-related adverse events occurred.

Comment: Dosing of the IV iron preparations iron sucrose, polymaltose and dextran requires the calculation of the total iron deficit using the Ganzoni formula, and those with a significant deficit may require multiple infusions due to daily dosing limitations. In this study, patients with IBD were randomised to a regime of iron sucrose calculated by the Ganzoni equation versus a ferric carboxymaltose regimen based on weight and haemoglobin. The ferric carboxymaltose regime was superior for the primary end point of achieving an increase in haemoglobin >2g/dL at week 12, and required significantly fewer infusions to reach this. This simplified ferric carboxymaltose regime may permit more efficient and effective dosing of IV iron supplementation.

Intravenous versus oral iron for the treatment of anemia in inflammatory bowel disease: A systematic review and meta-analysis of randomized controlled trials[29]

Authors: Bonovas S et al.

Summary: In a systematic review and meta-analysis, researchers compared five RCTs of IV versus oral iron supplementation for anaemia in a total of 694 adult IBD patients. IV iron had greater efficacy than oral iron in increasing haemoglobin by ≥2.0 g/dL (OR 1.57; 95% CI 1.13-2.18). Adverse event- or intolerance-induced treatment discontinuation rates were lower with IV iron (OR 0.27; 95% CI 0.13-0.59) and gastrointestinal adverse events were also reported less commonly with IV iron. However, serious adverse events were more frequent with IV iron (OR 4.57; 95% CI 1.11-18.8), although the majority of these were judged as unlikely or not related to study medication. Publication bias and between-study heterogeneity was not evident across all analyses, but risk of bias was high, because neither patients nor investigators were blinded to the intervention.

Comment: This recent meta-analysis included five RCT's comparing IV versus oral iron in patients with IBD. There was variability in terms of disease activity and baseline haemoglobin, but all studies reported a significantly greater proportion of patients who received IV therapy achieving a rise in haemoglobin >2 g/dL with a pooled OR of 1.57. In three studies, patients with a previous intolerance to oral iron were excluded, therefore discontinuation rates were low at just 10% overall and the superiority of IV therapy could therefore be underestimated. The rate of serious adverse events in the IV iron groups is something of a concern, though the majority were not felt to be treatment related.

Supplementation with oral vs. intravenous iron for anaemia with IBD or gastrointestinal bleeding: Is oral iron getting a bad rap?[38]

Authors: Rizvi S et al.

Summary: This review examined the physiology of iron supplementation, clinical data on oral dosing of iron, and compared IV and oral iron supplementation in IBD. While both IV and oral iron supplementation will raise haemoglobin levels in iron-deficiency anaemia, typical oral administration of iron may be excessive. IV iron does not appear to raise haemoglobin faster than oral administration. Adverse events associated with oral iron are probably related to relatively high dosages of elemental iron. New data suggest that low-dose iron has similar efficacy, with fewer adverse events. Both oral and IV iron are effective in IBD, and oral iron does not activate or exacerbate clinical symptoms.

Comment: Recommended dietary iron varies between 8 mg/day in adult men to 27 mg/day in pregnant women. Higher doses are required in the setting of iron deficiency, yet recommended doses of oral iron in the region of 150-200 mg/day may be excessive. Side effects from oral iron therapy appear to be dose dependant, and absorption is down-regulated as stores are replenished leaving more iron in the gut lumen as treatment progresses, increasing the risk of side-effects. This review article highlights several studies (none in IBD) in which low-dose oral iron therapy has been shown to be effective in resolving anaemia, with low rates of side effects. In IBD, concerns about worsening of disease activity with oral iron may have been overstated and may reflect use of excessively high doses. Perhaps oral iron is being underused in IBD, and lower dosing regimens may permit greater compliance and efficacy?

Ferric maltol is effective in correcting iron deficiency anaemia in patients with inflammatory bowel disease: Results from a phase-3 clinical trial program[16]

Authors: Gasche et al.

Summary: This 12 week, placebo-controlled, multicentre, phase III clinical trial examined ferric maltol (30 mg twice daily) as a novel oral iron therapy in 128 adult patients with quiescent or mild-to-moderate UC or CD and mild-to-moderate anaemia (9.5-12.0 g/dL in females and 9.5-13.0 g/dL in males) who had failed previous oral iron supplementation. In total, 55 (86%) ferric maltol and 53 (83%) placebo recipients completed the trial, and greater improvements in mean haemoglobin were observed with ferric maltol at 4 (1.04 g/dL), 8 (1.76 g/dL) and 12 (2.25 g/dL) weeks (all $p < 0.0001$). After 12 weeks, haemoglobin was normalised in two-thirds of patients. Ferric maltol had a safety profile comparable to placebo, with no impact on IBD severity.

Comment: Traditional oral iron preparations (sulphate, gluconate and fumarate) deliver high doses of iron to the gastrointestinal tract, but due to the limited absorptive capacity the large majority is unabsorbed and undergoes oxidation in the gastrointestinal tract. This leads to the formation of reactive oxygen species, which may account for many of the adverse gastrointestinal symptoms encountered. Ferric maltol is a novel oral iron formulation that is believed to allow more efficient uptake of iron, which can be achieved at a relatively low daily dose. In these phase III trials, two-thirds of patients with IBD, who had previously failed oral iron therapy, achieved a normalisation of haemoglobin when prescribed 60 mg of ferric maltol/day versus placebo. Ferric maltol was equally efficacious across both UC and CD and in quiescent and mild/moderate disease. Adverse events did not differ between treatment and placebo groups except for constipation in the treatment arm. This novel agent may prove to be a useful tool in the management of iron deficiency in IBD and avoid the need for IV agents.

Experts' concluding comments:

Iron deficiency anaemia is an important cause of morbidity in patients with IBD and warrants close monitoring and therapy when indicated. Concerns around oral iron exacerbating IBD may be overstated, but compliance with oral therapy remains a problem. IV therapy would appear to be superior and overcomes issues of compliance, but involves the inconvenience of visiting a health facility for parenteral administration and is costlier than oral therapy. An individualised, patient-centred approach should permit the correct choice of therapy to maximise compliance, convenience and efficacy, whilst minimising expenditure where possible.

TAKE-HOME MESSAGES[10,15]

- Anaemia and iron deficiency are very common in IBD
- Before treatment is initiated, a complete evaluation of the etiology of the anaemia must be carried out
- Oral iron may be used if the IBD is inactive, the anaemia is mild and oral iron is tolerated
- IV iron infusion is a simple therapy with a significant positive impact on quality of life in patients with IBD
- Parenteral iron should be used as first-line treatment in patients with clinically active IBD, with previous intolerance to oral iron, with haemoglobin levels <10 g/dL, and in patients requiring erythropoiesis-stimulating agents
- IV iron should be used when a quick response is required
- Rapid infusions (15 mins) are possible with ferric carboxymaltose
- Ferric carboxymaltose is the current standard at many sites
- Erythropoietin may be required in a small number of patients with functional iron deficiency
- Blood transfusion should be used rarely – the trigger should be a haemoglobin level < 7g/dL (or above if symptoms or particular risk factors are present)
- Blood transfusions should be followed by IV iron supplementation.

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