

# Iron deficiency anaemia: pathophysiology, assessment, practical management

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## ABSTRACT

The WHO has recognised iron deficiency anaemia (IDA) as the most common nutritional deficiency in the world, with 30% of the population being affected with this condition. Although the most common causes of IDA are gastrointestinal bleeding and menstruation in women, decreased dietary iron and decreased iron absorption are also culpable causes. Patients with IDA should be treated with the aim of replenishing iron stores and returning the haemoglobin to a normal level. This has shown to improve quality of life, morbidity, prognosis in chronic disease and outcomes in pregnancy. Iron deficiency occurs in many chronic inflammatory conditions, including congestive cardiac failure, chronic kidney disease and inflammatory bowel disease. This article will provide an updated overview on diagnosis and management of IDA in patients with chronic conditions, preoperative and in pregnancy. We will discuss the benefits and limitations of oral versus intravenous iron replacement in each cohort, with an overview on cost analysis between the different iron formulations currently on the market.

## INTRODUCTION

The WHO has recognised iron deficiency anaemia (IDA) as the most common nutritional deficiency in the world, with 30% of the population being affected with this condition.<sup>1</sup> While IDA is more prevalent in children and women, adult men are also susceptible depending on their socioeconomic status and health conditions.<sup>2</sup> Although the most common causes of IDA are gastrointestinal (GI) bleeding and menstruation in women, decreased dietary iron intake and absorption are also culpable causes.<sup>3</sup>

Iron is required for various cellular functions, including but not limited to enzymatic processes, DNA synthesis, oxygen transport and mitochondrial energy generation.<sup>4 5</sup> As such, the symptoms of IDA can vary over a wide range. Shortness of breath, fatigue, palpitations, tachycardia and angina can result from reduced blood oxygen levels. This resultant hypoxemia can subsequently cause a compensatory decrease in intestinal blood flow, leading to motility disorder,

malabsorption, nausea, weight loss and abdominal pain. Central hypoxia can cause headaches, vertigo and lethargy as well as cognitive impairment with several studies showing an improvement in cognitive functions once anaemia has normalised.<sup>6-9</sup> It is well known that IDA significantly affects quality of life (QoL)<sup>9</sup> with recent evidence demonstrating that treating IDA improves QoL, regardless of the underlying cause for anaemia.<sup>8 10</sup>

In this review, we will discuss the pathophysiology, diagnosis, treatment and complications in the management of IDA. The investigative criteria for IDA are beyond the scope of this article and have been comprehensively outlined in the recent British Society of Gastroenterology guidelines.<sup>11</sup>

## Pathophysiology

Iron is an essential element and is controlled primarily by dietary intake, intestinal absorption and iron recycling.<sup>12</sup> Dietary iron can be found in two forms: haem and non-haem iron. Haem iron is easily absorbable and arises from haemoglobin (Hb) and myoglobin in the form of animal meat, poultry and fish. Non-haem iron is mostly found in plant food but is not as easily absorbable. Compounds such as phytate, oxalate, polyphenols and tannin, which are found in plants, diminish the uptake of non-haem iron, as do some drugs, such as proton pump inhibitors.<sup>13 14</sup> Ascorbic acid, citrate and gastric acid, conversely, facilitate iron absorption.<sup>15</sup> In a healthy diet, approximately 5–15 mg of elemental iron and 1–5 mg of haem iron are ingested daily although only 1–2 mg is ultimately absorbed into the intestine, predominantly in the duodenum and proximal jejunum.<sup>16</sup> Please see figure 1 for details on the iron absorption pathways.

## Assessment and diagnosis

The WHO defines anaemia as blood Hb level below 130 g/L in men and 120 g/L in women.<sup>1</sup> In isolated iron deficiency, serum



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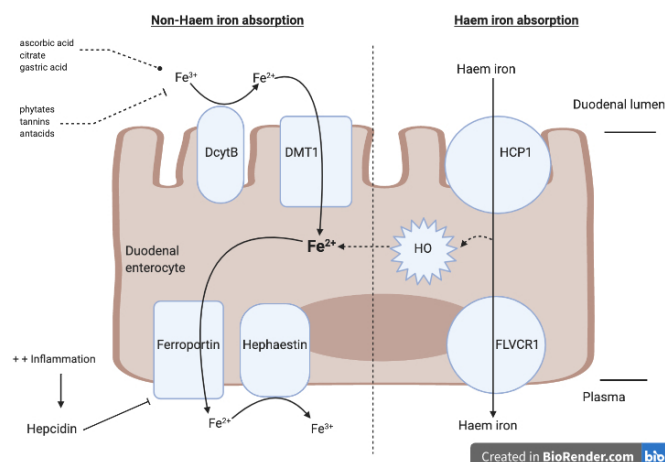
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**Figure 1** The two different iron absorption pathways. Non-haem absorption pathway (left): insoluble ferric iron ( $\text{Fe}^{3+}$ ) is reduced to absorbable ferrous iron ( $\text{Fe}^{2+}$ ), which is carried out by the enzyme duodenal cytochrome B (DcytB). The divalent metal transporter 1 (DMT1) imports  $\text{Fe}^{2+}$  across the apical surface and into the cell, which can then be either stored as ferritin or exported into circulation through ferroportin. Prior to exiting the enterocyte,  $\text{Fe}^{2+}$  must be oxidised back to  $\text{Fe}^{3+}$  by hephaestin or ceruloplasmin. Haem absorption pathway (right): the haem carrier protein (HCP1) transports haem iron directly into the enterocyte. Once inside the enterocyte, haem iron can either be released into plasma via the haem exporter FLVCR1 or be converted back into  $\text{Fe}^{2+}$  via the haem oxidase (HO) enzyme. The ferroportin receptor then releases  $\text{Fe}^{2+}$  into the plasma. Hepcidin, a hepatic peptide hormone, controls ferroportin, the sole iron exporter, by promoting its endocytosis. Hepcidin production and circulation are regulated by plasma iron concentration and iron stores. Hepcidin is increased in the presence of inflammation, which then promotes the degradation of ferroportin and subsequently impairs the exportation of cellular iron into plasma. Figure taken with permission from Kumar and Brookes.<sup>84</sup>

ferritin (the storage molecule for iron) should be less than 30  $\mu\text{g/L}$ .<sup>17</sup> However, ferritin is an acute phase protein and can be increased in the presence of inflammation.<sup>18</sup> Thus, if there is evidence of concomitant inflammation, such as elevated C reactive protein, ferritin less than 100  $\mu\text{g/L}$  is indicative of IDA.<sup>19</sup> Transferrin, the iron transporter, is generally elevated; however, it is a negative acute phase protein and, therefore, can be normal or reduced in chronic inflammatory states.<sup>20</sup> Serum iron and transferrin saturations (TSAT) will be reduced with TSAT less than 20% required for the diagnosis of IDA.<sup>17</sup> See table 1 for the breakdown of diagnostic criteria for IDA. It is crucial to note that iron deficiency should not be excluded in the presence of a normal Hb as a significant amount of iron must be lost before the Hb levels begin to decline. Thus, a low mean corpuscular Hb with a normal Hb or an increase in red cell distribution width signifies mild iron deficiency without anaemia.<sup>21</sup>

## Management

Patients with IDA should be treated with the aim of replenishing iron stores and returning the Hb to a normal level.

**Table 1** Diagnostic criteria for iron deficiency anaemia

Serum markers	Diagnosis for IDA
Haemoglobin	<130 g/L males <120 g/L females <110 g/L in pregnancy
Ferritin*	<30 $\mu\text{g/L}$ if no inflammation <100 $\mu\text{g/L}$ if inflammation
Transferrin†	Raised
Total iron binding capacity	Raised
Iron	Reduced
Transferrin saturations	<20%
Mean corpuscular volume	Low

\*Is an positive acute phase protein and can be raised in inflammatory conditions.

†Is a negative acute phase protein and can be normal or reduced in inflammatory conditions.

IBD, inflammatory bowel disease.

This has been shown to improve QoL, morbidity, prognosis in chronic disease and outcomes in pregnancy.<sup>22</sup> Iron replenishment can occur via three routes: oral iron, parenteral oral and transfusion of packed red cells. Each route has its benefits and limitations, which will be discussed below in greater detail.

## Conventional oral iron formulations

The British Society of Gastroenterology recommends ferrous preparations, specifically ferrous sulphate, as first-line therapy for iron replenishment as they are cheap, have good bioavailability, available in multiple preparations and have been shown to replenish iron stores and correct anaemia effectively.<sup>11</sup> However, there are also many limitations to their use, with the most common being the frequency and severity of side effects. A systematic review demonstrated that GI side effects were the most problematic with constipation being the most frequent complaint, followed by nausea and diarrhoea.<sup>23</sup> This will have a resultant effect on patient adherence, likely leading to cessation and, thus, inadequate treatment.<sup>24</sup>

The appropriate dosing of ferrous iron preparations is also a contentious issue between clinicians. To adequately replenish iron stores, therapeutic treatment of IDA was initially felt to require 200 mg of iron sulphate 2–3 times per day in order to raise Hb by 20 g/L over a 4-week period, with treatment continuing for 3 months.<sup>25</sup> However, the daily doses of elemental iron should not be greater than 100 mg/day<sup>26</sup> as the body can only absorb 10–20 mg of iron per day.<sup>26</sup> It should be noted that 200 mg of ferrous sulphate is equivalent to 65 mg of elemental iron.<sup>27</sup>

A recent study compared oral iron dosing regimens in women with mild anaemia with divided daily, once daily and alternate-day dosing. The results demonstrated superiority with alternate-day dosing, with 33% greater fractional iron absorption over 14 doses.<sup>28</sup> In addition,

a randomised trial of elderly patients with IDA received 15 mg, 50 mg or 150 mg of elemental iron per day. After 2 months, the mean increase in Hb was the same in all groups (1.4 g/dL); however, adverse effects were significantly greater with higher doses.<sup>29</sup> It is, therefore, an evolving view that a single daily dose (40–60 mg) or a slightly higher alternate-day dose (80–100 mg) is the preferred dosing regimen in order to reduce the side effects and optimise the proportion of elemental iron absorbed.<sup>28–30</sup>

Sodium feredetate is a water-soluble EDTA compound with higher bioavailability than the ferrous iron salt preparations. In the UK, it is available as a liquid preparation (Sytron); however, it is also available in tablet form (Ecofer, not currently licensed in the UK) often in combination with B12 and folate.<sup>31</sup> In a study looking at treatment of IDA in pregnant women, sodium feredetate increased Hb by 1.28 g/dL after 1 month of treatment and 2.11 g/dL after 2 months of treatment. This was in comparison to the group of women who received ferrous sulphate, where the mean Hb rose by 1 g/dL after 1 month and 1.58 g/dL after 2 months. As well as a significantly greater increase in Hb, there were significantly fewer side effects seen with sodium feredetate than ferrous sulphate.<sup>32</sup> This study also highlighted the improved bioavailability of sodium feredetate as this cohort was given one 231 mg tablet once per day for 2 months (equivalent to 33 mg of elemental iron) compared with the ferrous sulphate cohort who were given 200 mg tablets two times per day for 2 months (equivalent to 60 mg of elemental iron).

### Novel oral iron formulations

Ferric maltol, a novel preparation, is a non-salt oral iron formulation composed of stable ferric iron complexed with a sugar derivative, tri-maltol. It is licenced in the European Union and the USA and sold under the brand names Feraccru and Accrufer, respectively. When absorbed, the maltol ligand remains complexed to iron, which reduces the formation of free iron and facilitates iron transport across the enterocyte.<sup>33</sup> This subsequently increases the bioavailability of iron such that lower doses of elemental iron are required to treat IDA compared with the ferrous iron preparations.<sup>34</sup> Furthermore, ferric maltol has been shown to have less of an effect on the gut microbiome.<sup>35</sup> Studies on the use of ferric maltol has been limited to patients with inflammatory bowel disease (IBD), with results demonstrating improvement in Hb levels beyond 12 weeks with sustained normal Hb levels up to 64 weeks when compared with placebo.<sup>36 37</sup> When compared with intravenous ferric carboxymaltose, however, ferric maltol was shown to be inferior and did not meet the primary endpoint of increasing Hb by 2 g/L or Hb normalisation by 12 weeks (85% vs 68%, respectively).<sup>38</sup>

Finally, sucrosomial iron is an innovative oral iron-containing carrier, in which ferric pyrophosphate is within a phospholipid bilayer membrane forming the 'sucrosome', creating a gastroresistant complex, which

can be transported to the intestinal mucosa where it is absorbed without free iron interacting with the gut wall.<sup>39 40</sup> This unique structure protects iron from the acidic environment in the stomach, increases intestinal epithelial absorption and ensures high bioavailability while reducing the risk for potential adverse GI effects.<sup>39</sup> Despite lower doses of elemental iron, this newer oral iron preparation (30–60 mg/day) has also shown greater efficacy in increasing Hb and ferritin concentrations compared with ferrous sulphate (105–210 mg/day), with a mean Hb increase in 2.7 g/dL and 1.4 g/dL, respectively, over a 12-week course of treatment.<sup>39</sup>

Recent studies have demonstrated sucrosomial iron to be non-inferior to parenteral iron in patients with anaemia secondary to coeliac disease, cancer, bariatric surgery and chronic kidney disease (CKD).<sup>41–43</sup> In a study looking at patients with IDA as a result of benign GI or gynaecological bleeding who had previously not responded to or not tolerated ferrous sulphate were randomised to receive a high dose of either sucrosomial iron or intravenous ferrous gluconate. Results demonstrated that patients were comparable at baseline and rise in Hb was not significantly different between the two groups, with the number of weeks required to achieve an Hb target value of 12 g/dL was four in the sucrosomial iron group and 3.5 in the ferrous gluconate group.<sup>44</sup>

### Intravenous iron

An alternative to oral iron supplementation is parenteral administration. Intravenous iron is the preferred route of administration in some patients and is increasingly favoured due to its rapid correction of Hb, fewer side effects and improved safety profile. The primary advantage of intravenous iron is that it bypasses the GI tract absorption, thereby avoiding further mucosal aggravation and inflammation and producing less side effects.<sup>45</sup> Clinicians also do not have to worry about patient's adherence to medication.

There are a variety of intravenous iron preparations with selection of the agent dependent on multiple factors including cost considerations, patient and physician preference and product availability. It is important to note that clinical studies of the various formulations follow different protocols, and as of yet, there are no large head-to-head trials between these formulations comparing efficacy and safety profile.

Older intravenous iron preparations such as high-molecular weight dextran iron (Dexferrum) have been discontinued due to their unfavourable safety profiles with relatively high incidence of anaphylaxis.<sup>46</sup> The lower molecular weight dextran compounds such as Cosmofer are, however, still in use and have been shown to be effective with a much lower incidence of anaphylactoid reactions.<sup>47</sup> While there has not been a study comparing the different preparations, a meta-analysis looking at the overall rate of anaphylaxis with intravenous dextran was 0.61%,<sup>48</sup> which is significantly greater than with the newer non-dextran intravenous preparations.<sup>49</sup>





Ferric derisomaltose (Monofer) is an alternative intravenous iron preparation, which is often preferred to Cosmofer due to its shorter infusion time, thereby optimising the use of medical infusion units and nursing time as these drugs are often given as day-case procedures. Monofer is also preferred by some as it can be given as one infusion rather than two infusions. Ferric carboxymaltol (Ferinject) is a preparation widely used in the UK. It can be safely administered at a single dose of 1000 mg within 15 min; however, two infusions may be required in some patients, depending on their weight and Hb levels. Finally, iron sucrose (Venofer) is given by a slow injection of 100–200 mg 2–3 times a week.<sup>50</sup> It has been shown to be effective, although a comparison study showed Ferinject to be superior. In this study, Ferinject was associated with a higher rate of achieving a 2 g/dL increase in Hb concentration in comparison to iron sucrose by a relative risk of 1.65.<sup>51</sup> While Venofer has been extensively studied, the major drawback in its use is the need for multiple infusions, which can not only be less acceptable to patients but also made difficult for overstretched healthcare services.

### Red blood cell transfusion

It is advised that transfusions should be reserved for patients with severe anaemia, haemodynamically unstable and/or have associated comorbid conditions.<sup>26</sup> However, while severe anaemia is defined as Hb <70 g/dL, many of these patients may be haemodynamically stable and rather have chronic anaemia, remaining asymptomatic. Although a unit of blood contains approximately 200 mg of iron,<sup>32</sup> these patients are very likely to require further iron supplementation to adequately replenish their

iron stores, particularly if the cause for their anaemia is chronic and not easily treatable, for example, advanced malignancy or haematological disease.

Clinicians are rightly reluctant to transfuse patients unnecessarily as it is associated with not insignificant risks. These include an increased mortality with liberal blood transfusion in the setting of upper GI bleeding.<sup>52</sup> There is also increased incidence of transfusion-related reactions. This includes the risk of Transfusion Related Acute Lung Injury, which is one of the most serious reactions, the incidence of which is approximately 1 in 5000 transfusions.<sup>53</sup> Furthermore, there remains a small risk for transmitting infections, both viral and bacterial.<sup>54–56</sup>

## Considerations in management

### Comorbidities

IDA occurs in many chronic inflammatory conditions, including congestive cardiac failure (CCF), CKD and IBD (table 2). To complicate matters, symptoms such as fatigue are commonly seen in these conditions, which can mimic and be confused with symptoms of IDA. Consequently, the management of IDA can often be overlooked. Untreated IDA can have greater consequences in these conditions causing an exacerbation of the underlying disease.<sup>6</sup>

### Congestive cardiac failure

In CCF, IDA is one of the most prevalent comorbid conditions<sup>57</sup> and can be a result of multiple factors including reduced appetite, increased GI blood losses as a result of antiplatelet or anticoagulant medication and decreased GI absorption due to oedema.<sup>58</sup>

**Table 2** A list of common conditions and patient groups who have an increased risk of developing iron deficiency anaemia

Background	Cause of iron deficiency anaemia	Cause of blood loss	Recommended route of iron replacement
Congestive cardiac ailure	Poor nutrition Decreased GI absorption	Antiplatelet and/or anticoagulant use	Intravenous
Chronic kidney disease		Dialysis and frequent blood sampling	Intravenous
Inflammatory bowel disease		Chronically inflamed and ulcerated bowel	Intravenous
Elderly		Medications (antiplatelet, anticoagulant, anti-inflammatories, anti-depressants)	Oral
Malignancy	Poor nutrition Loss of healthy blood cells Damage to the bone marrow	Bleeding tumour	Intravenous
Surgery	Dependent on cause for surgery requirement	Excessive bleeding either pre and/or post-operatively	Intravenous or oral
Pregnancy	Poor nutrition Increased iron demands to mother and fetus	–	Intravenous or oral

The cause for iron deficiency anaemia, including causes for increased blood loss, and the recommended route of iron replacement are listed.

The median dose of iron needed to replete iron sufficiently in patients with CCF with IDA is 1000mg.<sup>59</sup> If patients were given ferrous sulphate, the first-line oral preparation, the bioavailability is only 10% at best,<sup>60</sup> and, thus, patients would need a minimum of 50 days at a dose of 200mg/day to correct the iron deficit. Realistically, considering missed doses or non-adherence, it can take up to 6 months to adequately replenish iron stores.<sup>58</sup> Thus, intravenous iron should be considered first line for the treatment of iron deficiency in CCF.<sup>6</sup> The Ferinject Assessment in Patients with Iron Deficiency and Heart Failure (FAIR-HF) and Ferric Carboxymaltose Evaluation on Performance in Patients with Iron Deficiency in Combination with Chronic Heart Failure (CONFIRM-HF) trials demonstrated the benefit of ferric carboxymaltose compared with placebo in correcting IDA by improving exercise capacity, cardiac function, symptom severity and QoL.<sup>61</sup>

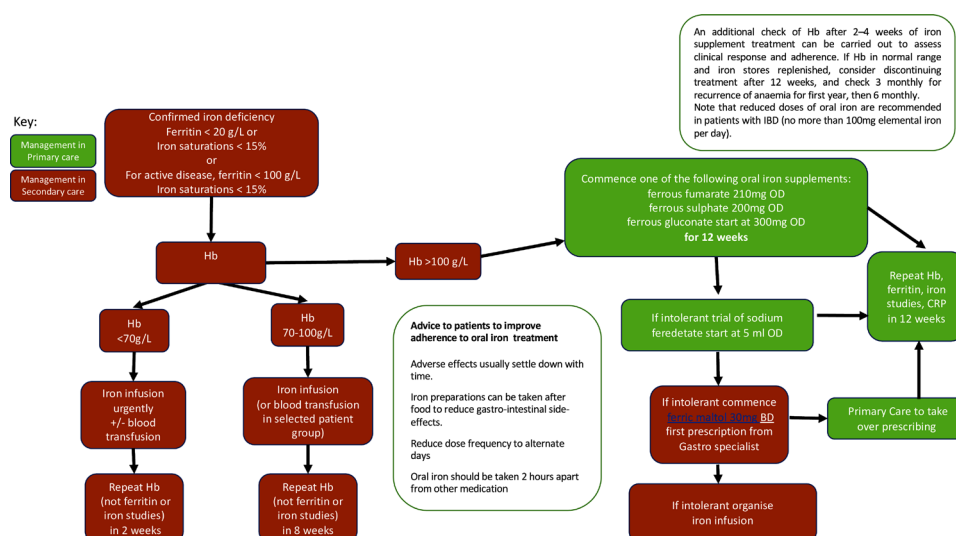
### Chronic kidney disease

The causes of IDA in CKD are similar to those in CCF, namely, reduced GI iron absorption, poor nutrition and blood loss caused by dialysis and frequent blood sampling. A recent meta-analysis and systematic review demonstrated intravenous iron to be more effective than oral iron in treating IDA in CKD, regardless of requirement for dialysis.<sup>6 62</sup> The Kidney Disease: Improving Global Outcomes clinical practice guidelines also recommend intravenous iron as first-line treatment for patients with stage 5 CKD.<sup>63</sup> However, ferric citrate might be an alternative oral preparation with a recent trial of 203 patients given 1g three times per day showing fewer hospitalisation rates and lower incidence of death, dialysis or transplantation.<sup>64</sup> Despite the evidence provided for intravenous preparations, oral iron remains first-line therapy for many clinicians and patients as it is readily available, inexpensive and avoids the need for intravenous access, which can cause injury to blood vessels

that may be needed in the future for critical vascular access.<sup>65</sup> Furthermore, there are concerns regarding potential side effects with intravenous iron including anaphylaxis, hypersensitivity, susceptibility to infections and cardiovascular events, hypophosphataemia and iron overload.<sup>66</sup> While human erythropoietin (EPO) and EPO-stimulating agents (ESA) have been in use for decades, they are associated with worsening hypertension, seizures and dialysis access clotting.<sup>67 68</sup> Moreover, ESA has not shown to reduce adverse outcomes associated with anaemia, including mortality rate, hospitalisations and progression of kidney disease.<sup>69</sup>

### Inflammatory bowel disease

IDA has been acknowledged as one of the most common extra intestinal manifestations of IBD.<sup>20</sup> Impaired GI iron absorption is caused by chronically inflamed bowel, chronic blood losses, bowel resection and malnutrition.<sup>6</sup> Improvement in iron status through treatment with intravenous iron has led to significant improvement in QoL in patients with IBD.<sup>10</sup> Adverse effects from oral iron are well recognised but have greater consequences in patients with IBD. Absorption from the GI tract is limited (on average 10%–20% of ingested amount) and unabsorbed iron is exposed to the ulcerated intestinal surface, which can cause further mucosal damage as well as changes to gut microbiota,<sup>70</sup> although it is not yet established whether oral iron exacerbates IBD inflammation beyond animal models. The European Crohn's and Colitis Organisation (ECCO) guidelines advise the use of intravenous iron as first-line therapy in patients with active disease, severe anaemia (Hb <100g/L), if previously intolerant to oral iron and for patients in need of concomitant treatment with EPO.<sup>26</sup> However, there is a place for both oral and intravenous iron in patients with IBD, which is further outlined in figure 2.



**Figure 2** Iron deficiency treatment pathway in patients with IBD patients as followed by the South East London Clinical Commissioning Group.<sup>85</sup> Hb, haemoglobin; IBD, inflammatory bowel disease.

### Malignancy

IDA is associated with multiple types of cancer, including GI (colorectal, pancreatic, oesophageal, gastric), lung, genitourinary (cervical, prostate, testicular), breast and haematological (lymphoma, leukaemia, myeloma).<sup>71</sup> In cancer patients, iron deficiency is associated with fatigue and weakness irrespective of the presence of anaemia.<sup>66</sup> Iron deficiency can occur frequently by means of chemotherapy-induced anaemia and anaemia of chronic disease.<sup>66</sup> Blood transfusions, ESA therapy and intravenous iron are the potential treatment options for IDA in patients with cancer. The aim is to improve QoL and reduce reliance on blood transfusions that are often associated with further multiorgan complications. Beneficial effects of ESAs are limited and both the European medicines agency and Food and Drug Administration have recommended restricting their use to patients with symptomatic anaemia and those undergoing specific chemotherapy.<sup>72</sup> A consensus of cancer experts suggest intravenous iron should be used over oral iron supplementation due to reduced efficacy and poor tolerance and adherence in the latter.<sup>72</sup> This is corroborated by a meta-analysis of 11 randomised studies, where intravenous iron had an improved haematopoietic response in chemotherapy-induced anaemia with no safety concerns and an overall reduction in blood transfusion requirement, compared with oral iron.<sup>73</sup>

### Elderly population

Another high-risk population are the elderly where prevalence of iron deficiency increases rapidly with age due to reduce oral intake, poor absorption and excess loss.<sup>74</sup> A meta-analysis of trial data shows treatment of iron deficiency with both oral and intravenous iron reduces blood transfusion requirements and increases Hb levels but does not significantly impact mortality.<sup>68</sup> Oral supplementation is recommended for treatment of IDA in this population, and lower doses of oral iron may be effective and better tolerated among elderly patients. For those whose oral treatment has been unsuccessful, intravenous treatment should be considered to avoid adverse effects and effectively treat anaemia. However, potential adaptations of oral therapy should also be considered such as liquid formulations or reducing dose frequency.<sup>74</sup>

### IDA in surgery

There is a growing field of evidence to focus on the impact of iron deficiency on morbidity and mortality in the perioperative period. Recently published national guidance recommends that IDA should be identified and treated pre and postoperatively,<sup>75</sup> whether that be via oral or intravenous iron supplementation. Intravenous iron is recommended for those who are unable to tolerate oral iron, those with functional iron deficiency and those with surgical procedures close to the time the IDA was diagnosed.<sup>75</sup> Further research is necessary to assess the impact of the timing of iron replacement prior to surgery.

### Pregnancy

Anaemia in pregnancy is defined as Hb <110 g/L with ferritin levels <100 µg/L.<sup>11</sup> The total iron loss in pregnancy approximately 1000 mg, and, thus, the recommended daily dietary allowance for iron in pregnancy is 27 mg compared with 8 mg in the adult non-pregnant population.<sup>76</sup> The usual recommended dose of elemental iron is 80 mg, which is equivalent to 250 mg of oral iron sulphate tablets.<sup>76</sup> Intermittent oral iron has been reported to be effective as daily iron dosing in raising Hb levels and is associated with a lower incidence of adverse effects.<sup>77</sup> However, a meta-analysis has demonstrated intravenous iron sucrose improved Hb (mean difference 7.17 g/L) and serum ferritin levels (mean difference 49.66 µg/L) while ferric carboxymaltose improved Hb levels (mean difference 8.52 g/L), compared with oral ferrous sulphate.<sup>78</sup> Furthermore, side effects were less common with the parenteral formulations, but included local pain, skin irritation and rarely allergic reactions.

### Adverse effects

As previously discussed, the common adverse effects of oral iron are well known among healthcare professionals and patients. The potential adverse effects of intravenous iron have more recently been publicised as they become further researched and understood. The rare adverse effect of hypersensitivity reactions has been known for some time and have dictated specialised protocols and training for healthcare professionals routinely administering intravenous iron.

Hypophosphataemia is an increasingly recognised adverse effect of intravenous iron. The risk of persistent hypophosphataemia and osteomalacia is possibly higher with ferric carboxymaltose than with the other intravenous iron preparations. A key mechanism is the carbohydrate moieties in ferric carboxymaltose inhibit degradation of fibroblast growth factor 23, resulting in greater renal loss of phosphate.<sup>79</sup> Phosphate replacement is an ineffective management strategy due to this mechanism as any phosphate replaced is lost through greater renal wasting.<sup>80</sup> Although the clinical significance is not yet fully understood, it is expected to have more of an effect on those patients requiring higher doses, repeat courses and are at a higher risk of electrolyte imbalances due to malnutrition.<sup>79</sup>

A less commonly recognised adverse effect is that of extravasation of intravenous iron that can cause long-lasting tattoo-like skin discolouration preceded by skin irritation and pain at the injection site. Though this adverse effect is considered to be rare (occurring at a rate of approximately 1.6%), the skin staining can last for several months after the initial infusion despite pharmacological interventions to resolve the reaction.<sup>81 82</sup> Though the extravasation of intravenous iron is not expected to cause harm, the long-lasting effects of the skin stain can have negative psychological and social impact on patients, so awareness of this phenomenon among healthcare professionals is imperative. Patients

**Table 3** Cost analysis per drug

Drug (brand)	Form	Time treatment course provided in (weeks)	Infusion time	Administration visits	Cost (£)
Ferrous sulphate*	Tablet	12	–	–	2.43
Ferrous gluconate*	Tablet	12	–	–	3.27
Ferrous fumarate*	Tablet	12	–	–	2.47
Sodium feredate (Sytron)**	Liquid	12	–	–	29.90
Ferric maltol (Ferracru)†	Capsule	12	–	–	142.80
Ferric carboxymaltose (Ferinject)‡	Injection	2	30	2	308.46
Ferric derisomaltose (Monofer)‡	Injection	2	30	2	339.00
Iron sucrose (Venofer)§	Injection	3	30	8	768.00
Iron dextran (Cosmofer)§	Injection	1	240	1	119.55

National Health Service (NHS) indicative price as per British National Formulary (BNF).

\*Cost based on one one tablet or 10 mL per day.

†Cost based on two capsules per day.

‡Based on 70 kg patient, with Hb <10 according to each summary of product characteristics.

§Based on 70 kg patient with Hb of 90 g/L.

Hb, haemoglobin.

should be informed of this potential adverse effect prior to administration of intravenous iron.

### Cost implications

It is important to consider both the cost of the impact of iron deficiency to the healthcare system and the cost of the individual treatments when assessing the overall cost of IDA management (table 3). Oral treatment with standard ferric salts is by far the lowest cost option with convenient administration and low drug cost (a 12-week course is approximately £2). Conversely, intravenous iron preparations can cost approximately £1400 per patient infusion when based on the highest iron requirement and including costs to the healthcare system for patient day-case admission. However, the most significant cost to the healthcare system is that of untreated IDA, which can result in emergency hospitalisation and multiple blood transfusions, approximately £1700 per admission on average. Brookes *et al* reviewed management of IDA in England between 2012 and 2018 and identified that £42.4million was spent on emergency hospital admissions. In comparison, £46million was spent on day case admissions, although four times as many patients were treated in the outpatient setting.<sup>83</sup> Though intravenous iron administration can seem more expensive than oral treatment, these findings strongly suggest that there is a need for a national strategy for standardising and streamlining elective intravenous iron administration to prevent more costly emergency admissions. For those who have not tolerated standard oral supplementation, ferric maltol may offer a more suitable alternative than intravenous iron. The cost of ferric maltol is significantly more than the standard oral iron (approximately £170 for a 12-week course) but much less than intravenous iron. If oral intolerance is the drive for choosing intravenous

treatment, then ferric maltol may offer an alternative choice with less potential adverse effects, although direct comparisons of this drug with other iron formulations still need to be studied.

### Looking to the future: service development and redesign

IDA is the most common nutritional disorder globally and is associated with multiple comorbid states with severe implications in QoL. Despite national guidance on managing IDA, there is still wide variability in current practices, not just between National Health Service trusts but also between clinicians and departments. Choosing between intravenous and oral iron therapies is dependent on many factors, including the therapy goal, response to prior therapy, patient preference, cost and ease of access to an infusion centre. A standardised pathway steered by evidence-based medicine can reduce this variance in care, while simultaneously supporting cost-effective anaemia management across and between the new integrated care systems.

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**Ethics approval** This study does not involve human participants.

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**Data availability statement** No data are available.

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