



# Iron deficiency anaemia

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Anaemia affects roughly a third of the world's population; half the cases are due to iron deficiency. It is a major and global public health problem that affects maternal and child mortality, physical performance, and referral to health-care professionals. Children aged 0–5 years, women of childbearing age, and pregnant women are particularly at risk. Several chronic diseases are frequently associated with iron deficiency anaemia—notably chronic kidney disease, chronic heart failure, cancer, and inflammatory bowel disease. Measurement of serum ferritin, transferrin saturation, serum soluble transferrin receptors, and the serum soluble transferrin receptors–ferritin index are more accurate than classic red cell indices in the diagnosis of iron deficiency anaemia. In addition to the search for and treatment of the cause of iron deficiency, treatment strategies encompass prevention, including food fortification and iron supplementation. Oral iron is usually recommended as first-line therapy, but the most recent intravenous iron formulations, which have been available for nearly a decade, seem to replenish iron stores safely and effectively. Hcpidin has a key role in iron homeostasis and could be a future diagnostic and therapeutic target. In this Seminar, we discuss the clinical presentation, epidemiology, pathophysiology, diagnosis, and acute management of iron deficiency anaemia, and outstanding research questions for treatment.

## Introduction

Iron deficiency occurs in two main forms: absolute or functional. Absolute iron deficiency arises when total body iron stores are low or exhausted; functional iron deficiency is a disorder in which total body iron stores are normal or increased, but the iron supply to the bone marrow is inadequate. Absolute and functional deficiencies can coexist. Functional iron deficiency can be present in many acute and chronic inflammatory states, and hepcidin—the master regulator of iron homeostasis—has a key role in pathogenesis. In this Seminar, we focus mainly on absolute iron deficiency.

## Clinical presentation

Patients with iron deficiency anaemia can present with symptoms that are associated with all anaemias, which are sometimes associated with specific signs due to iron deficiency (panel 1). Pallor of the skin, conjunctivae, and nail beds are common.<sup>1,11</sup> The diagnostic usefulness of these signs is increased when clinicians can ascertain whether their presence is a change from normal in the patient. Other symptoms and signs result from hypoxic functioning: fatigue,<sup>2</sup> exertional dyspnoea progressing to breathlessness at rest, vertigo, syncope,<sup>9</sup> headache,<sup>3</sup> tachycardia,<sup>8</sup> and a cardiac systolic flow murmur.<sup>7</sup>

### Search strategy and selection criteria

We searched the Cochrane Library, Medline, and Embase with the terms “anaemia”, “iron deficiency”, “epidemiology”, “pathophysiology”, “ferritin”, “serum soluble transferrin receptors”, “hepcidin”, “supplementation”, “fortification”, and “review”. We selected work published in any language, largely between Jan 1, 2010, and Dec 31, 2014, but did not exclude commonly referenced and highly regarded older publications. Our last search was on Jan 25, 2015. We also searched the reference lists of articles identified by this search strategy and selected those that we judged relevant.

In severe cases patients might have dyspnoea at rest, angina pectoris, and haemodynamic instability.<sup>8,11</sup>

Clinical features of iron deficiency anaemia depend on the severity of the anaemia, age, comorbidities, and chronicity and speed of onset. In some cases, anaemia is asymptomatic and diagnosed only after laboratory measurement of haemoglobin concentrations. Iron deficiency especially affects epithelial cells with a rapid turnover, causing dryness and roughness of the skin, dry and damaged hair, diffuse and moderate alopecia,<sup>4</sup> and koilonychia (spoon-shaped finger nails). Loss of tongue papillae occurs in patients with mild-to-moderate iron deficiency and is a good gauge of length of deficiency.

### Panel 1: Symptoms of iron deficiency anaemia

#### Very frequent

- Paleness (45–50%)<sup>1</sup>
- Fatigue (44%)<sup>2</sup>
- Dyspnoea
- Headache (63%)<sup>3</sup>

#### Frequent

- Diffuse and moderate alopecia (30%)<sup>4</sup>
- Atrophic glossitis (27%)<sup>5</sup>
- Restless legs syndrome (24%)<sup>6</sup>
- Dry and rough skin
- Dry and damaged hair
- Cardiac murmur (10%)<sup>7</sup>
- Tachycardia (9%)<sup>8</sup>
- Neurocognitive dysfunction
- Angina pectoris
- Vertigo

#### Rare

- Haemodynamic instability (2%)<sup>8</sup>
- Syncope (0–3%)<sup>9</sup>
- Koilonychia
- Plummer-Vinson syndrome (<0.1%)<sup>10</sup>

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Atrophic glossitis is noted in severe cases.<sup>5</sup> Iron deficiency has been reported to be associated with restless legs syndrome.<sup>6</sup> However, in a meta-analysis<sup>12</sup> evidence was insufficient to determine whether iron therapy is beneficial for restless legs syndrome ( $p=0.06$ ).<sup>12</sup>

Plummer-Vinson syndrome—which is also called Kelly-Paterson syndrome—is rare and characterised by dysphagia, iron deficiency anaemia, and oesophageal webs.<sup>10</sup> Accurate epidemiological data are not available but analysis of case reports suggests that about 90% of cases are in women, with a mean age at diagnosis of 47 years (range 28–80 years).<sup>10</sup> The syndrome is associated with an increased risk of squamous cell carcinoma of the pharynx and the oesophagus, which occurs in 3–15% of patients.<sup>10</sup> Iron deficiency seems to be dominant in the pathogenesis of Plummer-Vinson syndrome, and therefore iron supplementation is the main treatment.<sup>10</sup> Oesophageal webs can be endoscopically dilated if dysphagia persists despite iron supplementation. Yearly upper gastrointestinal endoscopies are recommended to detect prematurely neoplastic lesions.<sup>10</sup>

Whatever its cause, anaemia can negatively affect physical performance, particularly work productivity, in adults, as a result of both the reduced oxygen transport associated with anaemia and the reduced cellular oxidative capacity associated with iron deficiency.<sup>13</sup> In a 2013 systematic review,<sup>14</sup> a positive association was noted in older people (aged  $\geq 65$  years) between anaemia and global cognitive decline and incidence of dementia. Perinatal iron deficiency is associated with delayed neurocognitive development and psychiatric illness.<sup>15</sup> Even after iron repletion in infancy, cognitive abnormalities can persist at age 10 years.<sup>16</sup> Low body iron stores were significantly associated with low performances in cognitive executive planning function in 42 non-

anaemic undergraduate women ( $p=0.002$ ).<sup>17</sup> A meta-analysis<sup>18</sup> showed increased attention and concentration in children, adolescents, and women who received iron supplementation. Anger ( $p=0.007$ ) and fatigue ( $p=0.017$ ) were significantly higher in Japanese women with iron deficiency but who did not have anaemia, than they were in controls with healthy iron concentrations.<sup>19</sup>

## Epidemiology

In 2010, global anaemia prevalence was 32.9% (ie, more than 2.2 billion people were affected); iron deficiency was the most common cause.<sup>20</sup> WHO estimated that, between 1993 and 2005, worldwide prevalence of anaemia was 24.8% in the general population—from 12.7% in men to 47.4% in children aged 0–5 years. Prevalence was 30.2% in women, and 41.8% in pregnancy. 23.9% of people older than 60 years were anaemic.<sup>21</sup> Between 1995 and 2011, worldwide prevalence of anaemia decreased by 4–5% in children aged 0–5 years, non-pregnant women, and pregnant women aged 15–49 years.<sup>22</sup> Prevalence of anaemia varies hugely around the world.<sup>21</sup>

Iron deficiency is the most common nutritional deficiency, but robust, population-based studies are few. Thus, in US studies prevalence of iron deficiency ranges from 4.5% to 18.0%.<sup>23–25</sup> But at a global level, the lowest burden of anaemia associated with iron deficiency was noted in the USA and Canada (2.9% of envelope). In several regions—including central Asia (64.7%), south Asia (54.8%), and Andean Latin America (62.3%)—a very high proportion of the anaemia burden was caused by iron deficiency.<sup>20</sup>

Data for the epidemiology of iron deficiency anaemia are unreliable, especially because anaemia is often ascribed to iron deficiency, irrespective of its cause (table 1). WHO estimates that 50% of cases worldwide are due to iron deficiency,<sup>26</sup> but regional and subgroup disparities exist. In two studies from the past 3 years, prevalence of iron deficiency anaemia was roughly 20%.<sup>27,28</sup>

## Pathophysiology

Iron is an essential component of haemoglobin in red blood cells and of myoglobin in muscles, which contain around 60% of total body iron (appendix). It is also necessary for the functioning of various cellular mechanisms, including enzymatic processes, DNA synthesis, and mitochondrial energy generation. In adults, the body contains 3–5 g of iron; 20–25 mg is needed daily for production of red blood cells and cellular metabolism.<sup>29</sup> Because dietary intake is limited (1–2 mg per day), other sources are needed for iron homeostasis—eg, recycling of ageing erythrocytes in macrophages, exchange of iron in iron-containing enzymes, and iron stores.<sup>29</sup> About 1–2 mg of iron is lost daily as a result of menstrual bleeding, sweating, skin desquamation, and urinary excretion.<sup>29</sup> Because iron does not have an excretion regulation pathway, dietary intake, intestinal absorption, and iron recycling have to be finely regulated.

	Prevalence (%)
<b>Anaemia</b>	
General population <sup>20</sup>	32.9
Men (15–60 years) <sup>21</sup>	12.7
School-age children (>5 years) <sup>21</sup>	25.4
Elderly (>60 years) <sup>21</sup>	23.9
Preschool children (0–5 years) <sup>22</sup>	43.0
Non-pregnant women and girls (15–49 years) <sup>22</sup>	29.0
Pregnant women and girls (15–49 years) <sup>22</sup>	38.0
<b>Iron deficiency</b>	
Children (<2 years) <sup>23</sup>	9.0
Children (3–5 years) <sup>24</sup>	4.5
Adolescent girls (12–19 years) <sup>24</sup>	15.6
Women (20–49 years) <sup>24</sup>	15.7
Pregnant women and girls (12–59 years) <sup>25</sup>	18.0
<b>Iron deficiency anaemia</b>	
General population <sup>26</sup>	12.2
Hospital-based population <sup>27</sup>	23.0

Table 1: Prevalence of anaemia, iron deficiency, and iron deficiency anaemia

See Online for appendix

Dietary iron is available in two forms: haem and non-haem iron. Iron is complexed as Fe<sup>2+</sup> (ferrous iron) in haemoglobin in the haem form, which is present in animal food sources, such as meat, poultry, and seafood.<sup>30</sup> Non-haem iron (Fe<sup>3+</sup> or ferric iron) is present in the vegetarian diet (black tea, cacao, cereals, dried fruit, etc).<sup>30</sup> Haem iron is estimated to contribute 10–15% of total iron intake in meat-eating populations, but because it is generally better absorbed—with a rate of absorption estimated at 15–35%—than non-haem iron, it can account for more than 40% of total absorbed iron.<sup>31</sup>

In iron homeostasis, a small peptide called hepcidin, which is mainly secreted by hepatocytes and was first described in 2001 in mice with iron overload,<sup>32</sup> has a crucial role in the control of iron availability to tissues. Outside the liver, other cell types and organs, such as macrophages,<sup>32</sup> adipocytes,<sup>33</sup> the heart,<sup>34</sup> and the kidneys,<sup>35</sup> can produce hepcidin. In plasma, hepcidin is bound to  $\alpha$ 2-macroglobulin<sup>36</sup> and albumin,<sup>37</sup> and can be cleared via the kidney.<sup>37</sup> The main role of hepcidin is to control surface expression of FPN1 by binding to the protein, which is then internalised and degraded by lysosomes.<sup>37</sup> FPN1 is the only known iron-exporting protein, so after its degradation enterocytes, macrophages, and hepatocytes can no longer export iron, which is sequestered in these cells.

High expression of hepcidin decreases plasma iron concentrations; low expression increases concentrations. Hepcidin expression is upregulated by high concentrations of iron in the liver and plasma, inflammation, and physical activity<sup>38,39</sup> whereas it is downregulated by iron deficiency, erythropoiesis, hypoxia, and endocrine signals (testosterone, oestrogen, and growth factors). A new hormone called erythroferrone was identified in 2014. It is produced by erythroblasts in response to erythropoietin, and mediates hepcidin suppression during stress erythropoiesis.<sup>40</sup>

### Risk factors

Physiological and pathological conditions can promote iron deficiency anaemia (panel 2). The maximum absorption of iron from the diet is less than the body's requirements for iron, resulting in a risk of iron deficiency. In infants and young children (aged 0–15 years), rapid growth consumes the iron stores that accumulate during gestation, which can, in turn, lead to an absolute deficiency.<sup>41</sup> After childhood, adolescent girls are particularly at risk of iron deficiency anaemia, because of menstrual iron losses.<sup>42</sup> During pregnancy, iron needs are tripled because of expansion of maternal red cell mass and growth of the fetus and placenta. Daily iron supplementation is significantly associated with reduced risk of anaemia at term.<sup>43</sup> Mothers who breastfeed are less likely to be iron deficient than pregnant women because iron concentration in mature breastmilk is only 0.20–0.80 mg/L,<sup>56</sup> and most breastfeeders are amenorrhoeic. Regular blood donors are at increased risk of iron deficiency.<sup>44</sup>

### Panel 2: Physiological conditions and pathological disorders associated with iron deficiency anaemia

#### Physiological

- Infancy<sup>41</sup>
- Adolescence in girls<sup>42</sup>
- Pregnancy<sup>43</sup>
- Regular blood donation<sup>44</sup>
- Being an elite athlete<sup>39</sup>

#### Pathological

##### Blood loss

- Digestive tract: colonic carcinoma, gastric carcinoma, inflammatory bowel
- Diseases, ulcers, angiodysplasia, parasites<sup>45</sup>
- Gynaecological loss<sup>46</sup>
- Surgery
- Haematuria, epistaxis, haemoptysis
- Haemodialysis
- Non-steroidal anti-inflammatory drugs, aspirin

##### Malabsorption

- Coeliac disease<sup>47</sup>
- Gastrectomy
- *Helicobacter pylori*<sup>48</sup>
- Gut resection, atrophic gastritis, bypass gastric surgery, bacterial overgrowth<sup>45</sup>
- Interaction with food elements: tea, coffee, calcium, flavonoids, oxalates, phytates
- Pica syndrome, pagophagia
- Proton-pump inhibitors and H2 antagonists

##### Iron deficiency anaemia associated with anaemia of chronic disease

- Chronic heart failure<sup>49</sup>
- Cancer<sup>50</sup>
- Chronic kidney disease<sup>51</sup>
- Rheumatoid arthritis<sup>52</sup>
- Obesity<sup>53</sup>
- Inflammatory bowel diseases<sup>54</sup>

##### Genetic disorders

- Iron-refractory iron deficiency anaemia<sup>55</sup>
- Others (divalent metal transporter 1 deficiency anaemia, Fanconi anaemia, pyruvate kinase deficiency, etc)

In relation to diet, ferritin concentrations do not seem to differ between omnivores and vegetarians.<sup>42</sup> Some components of diet directly affect iron bioavailability. Phytates (found in cereals and vegetables), polyphenols (found in vegetables, fruits, some cereals and legumes, tea, coffee, and wine), calcium, and proteins inhibit iron absorption. By contrast, ascorbic acid and muscle tissue enhance absorption.<sup>31</sup>

Various drugs and abnormalities can lead to iron deficiency anaemia, including blood loss, malabsorption, chronic disease (so-called iron deficiency anaemia associated with anaemia of chronic diseases),<sup>57</sup> and genetic alterations. Blood loss is the most common, especially from the digestive tract. In UK guidelines,<sup>45</sup> the most common causes of blood loss were colonic carcinoma, gastric carcinoma, benign gastric ulceration, and angiodysplasia. In developing countries, gastrointestinal

	Healthy	Mild anaemia	Moderate anaemia	Severe anaemia
Boys and girls (0.5–4 years)	≥110	100–109	70–99	<70
Boys and girls (5–11 years)	≥115	110–114	80–109	<80
Boys and girls (12–14 years)	≥120	110–119	80–109	<80
Non-pregnant women and girls (15 years or older)	≥120	110–119	80–109	<80
Pregnant women and girls (≥15 years)	≥110	100–109	70–99	<70
Men and boys (15 years or older)	≥130	110–129	80–109	<80

Table 2: Haemoglobin concentrations (in g/L) for diagnosis of anaemia, by population

parasites such as *Trichuris trichiura* (whipworm) and *Necator americanus* (hookworm) account for about a third of iron deficiency anaemia.<sup>58</sup> Anthelmintic treatment given every 3 months to Zanzibari children decreased the incidence of anaemia by 59%.<sup>59</sup> Gynaecological loss is the next most frequent cause.<sup>46</sup> Excessive surgical blood loss without replacement can also lead to iron deficiency anaemia. Other blood losses, such as haematuria, epistaxis, or haemoptysis, occur much less frequently.

The most common causes of iron malabsorption are coeliac disease,<sup>47</sup> gastrectomy, bypass gastric surgery,<sup>60</sup> and *Helicobacter pylori* colonisation.<sup>48</sup> Uncommon causes of malabsorption are substantial gut resection, atrophic gastritis, and bacterial overgrowth, each of which cause less than 1% of iron deficiency anaemia.<sup>45</sup> Pica is a compulsive disorder characterised by an appetite for substances with no significant nutritional values (such as paper, clay, soil, glass, or sand) that can lead to iron malabsorption. A craving for ice, pagophagia, has similar effects. Many drugs are associated with iron deficiency anaemia, either by increasing blood loss (eg, non-steroidal anti-inflammatory drugs) or decreasing iron absorption (eg, proton-pump inhibitors and H2 receptor antagonists). Iron deficiency anaemia is frequently reported in chronic disorders,<sup>57</sup> including inflammatory bowel diseases (IBD),<sup>54</sup> chronic heart failure,<sup>49</sup> chronic kidney disease,<sup>51</sup> cancer,<sup>50</sup> rheumatoid arthritis,<sup>52</sup> and obesity.<sup>53,61</sup>

Anaemias caused by genetic defects are a large group of rare, heterogeneous disorders. The European Network of Rare Congenital Anaemias lists 62 rare anaemia subtypes,<sup>62</sup> including haemolytic anaemias and anaemias arising from mutations in genes that control duodenal iron absorption (eg, *SLC11A2*), systemic iron homeostasis (eg, *TMPRSS6*), or erythroid iron absorption and utilisation. Iron refractory iron deficiency anaemia is a microcytic anaemia that affects fewer than one in a million people.<sup>62</sup> It is caused by a defect in the *TMPRSS6* gene encoding matriptase-2, which has a key role in the downregulation of hepcidin. Hepcidin concentrations are increased in the disorder, leading to iron deficiency.<sup>55</sup> Oral iron is ineffective. Correction of iron refractory iron deficient anaemia by parenteral iron is partial and much slower than that in patients with acquired iron deficiency.<sup>55</sup> Some researchers recommend recombinant erythropoietin to

target a subnormal concentration of haemoglobin to avoid the risk of iron overload.<sup>55</sup>

## Diagnostic investigations

The diagnosis of anaemia is made after confirmation of a reduced blood haemoglobin concentration as shown by a full blood count. Thresholds to define anaemia depend on age, sex, pregnancy, altitude, and smoking. An adult man is deemed anaemic when his haemoglobin concentration is less than 130 g/L, whereas an adult woman is judged anaemic when her haemoglobin concentration is less than 120 g/L. In pregnancy, this cutoff is lowered to 110 g/L (table 2).<sup>63</sup>

Diagnosis of iron deficiency is somewhat complex, and use of several iron status indicators in combination seems to provide the best assessment of iron sufficiency. Several laboratory markers of iron status might be available (appendix). First, red cell indices on full blood counts might show a reduced mean cell haemoglobin, which corresponds to hypochromia, and a reduced mean cell volume, corresponding to microcytosis. Thresholds are not universally agreed, and disparities exist between laboratories.<sup>64</sup> Mean cell haemoglobin and volume are inexpensive, widely available, and sensitive measures, but become abnormal only in longstanding iron deficiency. These measures are also decreased in several chronic disease states, including haemoglobinopathies (such as thalassaemia) or sideroblastic anaemia. Moreover, mean cell volume could be normal in combined nutrient deficiency. In cases of microcytosis, haemoglobin electrophoresis is recommended in patients of appropriate ethnic background (people from Mediterranean countries, the Middle East, central Asia, India, southern China, and east Asia) to eliminate a haemoglobinopathy such as thalassaemia or sickle cell disease.<sup>45</sup>

In the absence of inflammation, serum ferritin measurement is the most specific test that correlates with total body iron stores. It is a universally available and standardised measurement. Iron deficiency is diagnosed below the cutoff of 15 µg/L in patients older than 5 years.<sup>26</sup> In a systematic review,<sup>65</sup> ferritin was the most effective test to detect iron deficiency.<sup>65</sup> However, other authors suggested that the diagnostic accuracy of ferritin could be improved by increasing the cutoff to 30 µg/L. The sensitivity then increased from 25% to 92%, compared with the cutoff value of 12 µg/L.<sup>66</sup> Specificity was unchanged at 98%.<sup>66</sup>

Ferritin concentrations are increased independently of iron status in acute and chronic inflammatory disorders, malignant disease, and liver disease—a serious diagnostic limitation. In these situations, patients with a ferritin concentration of 50 µg/L or higher could still be iron deficient.<sup>26,65</sup> In chronic kidney disease, cutoffs of 100 µg/L have been suggested,<sup>67</sup> and 200 µg/L in case of haemodialysis.<sup>68</sup> Other assays can be helpful in these disorders, such as serum iron and serum transferrin concentrations or total iron-binding capacity, which is needed to calculate the transferrin saturation.

In cases of iron deficiency, serum iron is reduced and total iron-binding capacity is increased, resulting in a substantial reduction in transferrin saturation (ie, the ratio of serum iron to total iron-binding capacity). The threshold of 16% is generally used to screen for iron deficiency,<sup>26</sup> but a threshold of 20% is used in the presence of inflammation.

Serum soluble transferrin receptors (sTfR) derive from proteolysis of the membrane transferrin receptor. This process shows tissue iron deficiency and inversely the amount of iron available for erythropoiesis. In case of iron deficiency, synthesis of transferrin receptors is increased, leading to a corresponding increase in sTfR. A substantial advantage of measurement of sTfR compared with other assays is that sTfR concentrations are not affected by inflammation.<sup>66</sup> Concentrations of sTfR can be raised in patients with disorders associated with increased erythropoiesis, such as haemolytic anaemia or chronic lymphocytic leukaemia, and in those who use recombinant human erythropoietin. Another limitation is the absence of standardised cutoffs worldwide, although UK guidelines have been published.<sup>68</sup>

In 2012, a meta-analysis<sup>69</sup> of ten studies of sTfR accuracy showed that the assay had a sensitivity of 86% and a specificity of 75%. In routine practice, measurement of sTfR is not needed for a diagnosis of iron deficiency anaemia. The ratio between these receptors and the logarithm of serum ferritin (ie, the sTfR–F index) seems to discriminate disease—particularly chronic disease—better than either test individually.<sup>70</sup> It is directly proportional to tissue deficit in patients with iron deficiency. When the sTfR–F index is low, anaemia is probably caused by chronic disease. When it is high, iron deficiency is probably the major cause of anaemia.<sup>71</sup> Although thresholds are not clearly defined, a ratio greater than 2–3 can be used to diagnose iron deficiency anaemia.<sup>57,72,73</sup> Limitations of this index are the same as those of sTfR.

Bone marrow aspiration is still thought of as the gold standard for diagnosis of iron deficiency. It is not affected by inflammation and is highly specific, but is invasive, uncomfortable for the patient, expensive, and affected by recombinant human erythropoietin. Thus, bone marrow aspiration is reserved for very specific cases, when other techniques are negative or conflicting.

In cases of iron depletion, zinc transport across the intestine increases. Thus, an increased concentration of zinc protoporphyrin in erythrocytes (>80 µg/dL) is associated with iron deficiency anaemia.<sup>26</sup> The ratio between zinc protoporphyrin and haem concentrations provides similar information.<sup>74</sup> Compared with bone marrow aspiration, zinc protoporphyrin assays had a sensitivity of 77·8% and specificity of 69·8%.<sup>75</sup> Disorders other than iron deficiency can lead to increased concentrations, such as infection, inflammation, lead poisoning, haemolytic anaemia, increased bilirubin concentrations, and haemodialysis. Zinc protoporphyrin

measurements are not widely available in most clinical laboratories, partly because of the difficulty of automation of the assay.

Measurement of the proportion of circulating hypochromic red cells as a proportion of total red blood cells is the most sensitive marker of iron deficiency in patients with chronic kidney disease—6% is the cutoff.<sup>76</sup> Unfortunately, a fresh blood sample is needed for this analysis, and automated analysers are not widely available. Reticulocyte haemoglobin content is a very early indicator of iron status, and shows available iron for erythropoiesis during the 3–4 days before measurement.<sup>77</sup> A reticulocyte haemoglobin content of less than 27·2 pg is diagnostic. But access to this assay is poor, and false normal values can occur in patients with raised mean cell volumes or thalassaemia.<sup>78</sup> Measurement of reticulocyte haemoglobin content is being incorporated into several cell counters (eg, Siemens, Sysmex, Beckman-Coulter).

### Acute and long-term management

The aim of treatment is to supply enough iron to normalise haemoglobin concentrations and replenish iron stores, and thereby to improve quality of life, symptoms, and the prognosis of many chronic disorders. Two distinct approaches exist: prevention strategies targeted at populations at risk and active iron supplementation approaches in confirmed iron deficiency anaemia.

On a global level, food-based approaches—ie, promotion of access to, and consumption of, iron-rich foods such as meat and organs from cattle, fowl, fish, and poultry, and non-animal foods such as legumes and green leafy vegetables—are recommended by WHO.<sup>26</sup> The bio-availability of iron can be increased by absorption enhancers, including ascorbic acid. Inhibitors of iron absorption—eg, calcium; phytates, which are essentially present in cereal; tannins, which are found in tea and coffee—should be reduced or removed from iron-rich meals. Tea can reduce iron absorption by 90%.<sup>79</sup> Deworming might increase people's haemoglobin concentrations.<sup>80,81</sup> Enrichment of food with iron is an effective public health intervention to improve the iron status of populations.<sup>82</sup> Iron should be incorporated in widely consumed food, organoleptic properties should not be changed, and prices should not increase. Rice is fortified in the Philippines, bread in Chile, and flour in Venezuela.<sup>82</sup>

After 6 months of breastfeeding, children need an additional source of iron to maintain adequate iron nutrition. WHO recommends micronutrient powders in children aged 6–23 months if the prevalence of anaemia is 20% or higher, with the aim of providing 12·5 mg elemental iron daily, preferably as ferrous fumarate. Thereafter, iron is added to children's daily food.<sup>82</sup> In a 2013 meta-analysis,<sup>83</sup> food fortification with micronutrient powder reduced anaemia by 31% and iron deficiency by 51% compared with placebo in children younger than 2 years.<sup>83</sup>

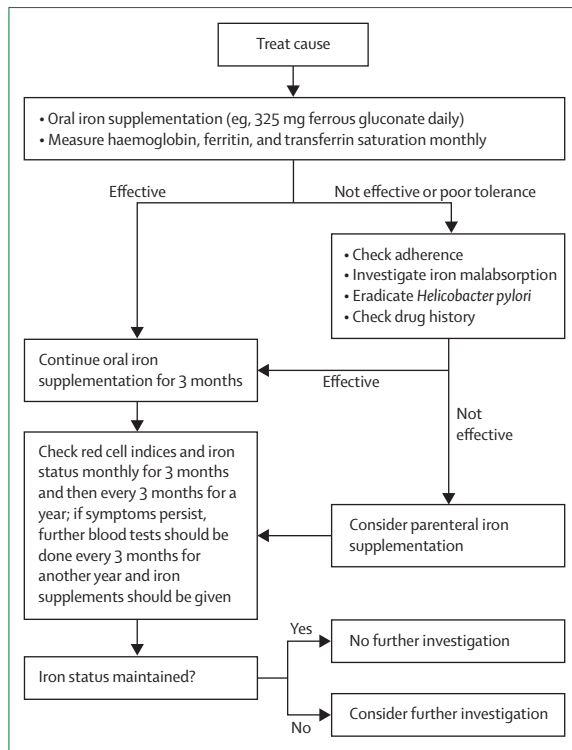


Figure: Algorithm for treatment of iron deficiency anaemia

### Iron supplementation

Iron supplementation is used in two clinical scenarios: to prevent iron deficiency anaemia in at-risk populations, or to treat patients with proven disease. In 2011, WHO recommended daily iron supplementation with 60 mg of elemental iron to prevent iron deficiency in menstruating adolescent girls and women where the prevalence of anaemia is 20%.<sup>84,85</sup> Similar recommendations were made for children aged 0–5 years (2 mg/kg daily) and children aged 5–12 years (30 mg daily).<sup>86</sup>

For therapeutic iron supplementation, four common iron preparations are available: ferrous sulphate, ferrous sulphate exsiccated, ferrous gluconate, and ferrous fumarate. No one compound seems better than the others. The usual dosage is 325 mg (corresponding to 65 mg of elemental iron) three times a day. But lower dosages—eg, 200 mg twice daily—seem as effective and are associated with fewer side-effects.<sup>45</sup> Iron absorption by enterocytes seems saturable; thus a dose of iron could prevent absorption of subsequent doses.

Ferrous sulphate should be taken between meals, and patients should avoid inhibitors of iron absorption when taking the dose. Although ascorbic acid can improve the bioavailability of dietary iron, it increases the frequency of side-effects associated with oral iron supplements, such as epigastric discomfort, nausea, diarrhoea, and constipation, because it increases the amount of ferrous iron downstream. Side-effects occur in roughly about 32% of patients according to a meta-analysis<sup>87</sup> of studies

in which oral and intravenous iron (ferric carboxymaltose) were compared,<sup>87</sup> and as many as 70% of patients in some studies.<sup>88,89</sup> The stool often turns black, which is not harmful, and treatment does not have to be interrupted.

When side-effects occur, iron can be taken with meals, but doing so decreases absorption to 40%. Alternatively, smaller doses could be taken between meals and at bedtime or ferrous sulphate could be replaced by 325 mg ferrous gluconate daily (35 mg of elemental iron). The reticulocyte count should rise as soon as 4 days after treatment is begun and reach a maximum at 7–10 days. Haemoglobin concentrations start rising by the second week of therapy. Historically, a 20 g/L improvement in haemoglobin concentration has been deemed an appropriate response to iron supplementation, but serum ferritin concentration and zinc protoporphyrin are significantly ( $p < 0.001$ ) correlated to haemoglobin, and can be used as markers of effectiveness.<sup>90</sup> Oral iron should be given for 3 months after iron deficiency has been corrected so that stores are replenished.

When patients do not respond to treatment, the diagnosis of iron deficiency anaemia should be reconfirmed and adherence should be assessed and improved. Then, the cause of iron deficiency should be corrected, if possible. Malabsorption of iron can occur, especially in cases of coeliac disease, bowel resection, or *H pylori* infection. True malabsorption can be diagnosed by giving an oral dose of liquid ferrous sulphate (50–60 mg iron) and measuring serum iron concentration 1–2 h later. A serum iron concentration of less than 100 µg per 100 mL suggests iron malabsorption. A meta-analysis<sup>91</sup> showed that eradication of *H pylori* accelerated the improvement of ferritin concentrations. However, this benefit was not maintained after 3 months.<sup>91</sup>

Iron chelates have also been assessed. Inulin, a natural fructose polymer, can be chelated with iron to enhance iron absorption within the colon.<sup>92</sup> Similar results were reported for bisglycinate iron<sup>93</sup> and liposomal iron.<sup>94</sup>

Parenteral iron is indicated when blood loss exceeds the absorptive capacity for iron, in case of iron malabsorption, or oral treatment is unsuccessful or poorly tolerated by the patient (figure). Six main forms of intravenous iron are available: iron sucrose, ferric gluconate, ferric carboxymaltose, iron isomaltoside-1000, ferumoxytol, and iron dextran (low-molecular-weight forms). These compounds comprise a core containing an iron salt, such as iron oxyhydroxide, surrounded by a carbohydrate shell. The compound is processed by the reticuloendothelial system. The iron is then released from the complex and either stored in ferritin or exported back to plasma, via ferroportin, and binds to transferrin. The kinetics of iron release from the complex varies according to the iron preparation. Iron is most tightly bound to iron dextran preparations, and most loosely bound to iron gluconate. The speed of release also determines how much iron can be given as a single dose.

Iron dextran products can be given in quantities of 1 g or more, whereas the maximum single dose of iron gluconate is 125 mg.

Intravenous iron replenishes iron stores more effectively than does oral iron post partum<sup>95</sup> and in several disorders, including inflammatory bowel disease<sup>96</sup> and chronic kidney disease.<sup>97</sup> In the FERGICor study,<sup>98</sup> a randomised, controlled, open-label, multicentre study of 485 patients with inflammatory bowel disease and iron deficiency anaemia, ferric carboxymaltose and iron sucrose were compared.<sup>98</sup> The primary endpoint—an increase in haemoglobin concentrations of 20 g/L or more—was achieved in 65·8% of patients in the ferric carboxymaltose group and 53·6% in the iron sucrose group ( $p=0\cdot004$ ).

High-molecular-weight iron dextran is associated with a higher frequency of serious anaphylactic reactions than are other preparations. In a review<sup>99</sup> of data from WHO and drug manufacturers, 31 deaths in the USA were associated with this preparation between 1976 and 1996. Thus, high-molecular-weight iron dextran has been withdrawn from the market. However, low-molecular-weight iron dextran and other newer formulations seem to have the same safety profile as ferric gluconate.<sup>100</sup> In a multicentre, crossover, randomised, double blind, placebo-controlled prospective study of 2534 patients undergoing haemodialysis, the frequency of drug intolerance was 0·44% with ferric gluconate (95% CI 0·21–0·71%) and 0·1% with placebo ( $p=0\cdot02$ ).<sup>101</sup> No difference was noted between groups in the frequency of serious adverse events. A life-threatening event (immediate reaction necessitating resuscitation measures) occurred in the ferric gluconate group (0·04%, 95% CI 0·00–0·22%).

35% of patients given iron sucrose have mild side-effects (abdominal pain, nausea, headache, diarrhoea); the frequency of serious adverse reactions is low (0·03–0·04%).<sup>45</sup> In a meta-analysis<sup>87</sup> the safety profile of ferric carboxymaltose was assessed, and serious adverse events occurred in roughly 3% of patients, which did not differ significantly from the frequency in patients given placebo.<sup>87</sup> About 0·4% of patients given ferric carboxymaltose died—which was not significantly different from the rate of death in patients given placebo. Ferumoxytol is a superparamagnetic iron oxide coated with carbohydrate that is used in iron deficiency anaemia and as a contrast agent for MRI. It has been approved for use in patients with chronic kidney disease in the USA since 2009, and in Europe since 2012. According to a report<sup>102</sup> from the Canadian Agency for Drugs and Technologies in Health, ferumoxytol seems as effective as other intravenous iron formulations.

Patients with self-limiting minor infusion reactions are often inappropriately given pressors and anti-histamines, which probably cause most of the serious adverse events associated with intravenous iron. The European Medicines Agency's Committee for Medicinal Products for Human Use concluded that the benefits of intravenous iron exceed the risks provided that adequate

measures are taken to minimise allergic reactions.<sup>103</sup>

A guideline with recommendations about the management and prevention of hypersensitivity reactions to intravenous iron was published in 2014.<sup>104</sup> The potential of all intravenous iron preparations to exacerbate oxidative stress and increase susceptibility to infections is of concern. In their meta-analysis,<sup>105</sup> Litton and colleagues<sup>105</sup> reported a significant increase in the risk of infection with intravenous iron (relative risk 1·33, 95% CI 1·10–1·64) compared with oral or no iron supplementation. We will not discuss alternative treatments, such as blood transfusions, but refer readers to Goodnough and colleagues' 2013 review.<sup>106</sup>

### Follow-up

Once the cause of iron deficiency anaemia has been treated and haemoglobin concentrations are healthy, full blood count and markers of iron status should be measured regularly. The British Society of Gastroenterology recommends monthly measurements for 3 months, and then every 3 months for a year.<sup>45</sup> If symptoms persist, further blood tests should be done every 3 months for another year, and iron supplements should be given. If haemoglobin or red cell indices cannot be maintained in this way, further investigations are necessary.<sup>45</sup>

### Outstanding research questions

Because oral iron is associated with gastrointestinal side-effects, new formulations have been developed. In a trial<sup>107</sup> of patients with inflammatory bowel disease and iron deficiency anaemia, ferric maltol was more effective than placebo at increasing haemoglobin at 12 weeks ( $p<0\cdot001$ ), and had a similar safety profile. In non-dialysis-dependent patients with chronic kidney disease, oral haem iron polypeptide had similar efficacy to intravenous iron sucrose in maintaining haemoglobin, with no differences in adverse events.<sup>108</sup> Many studies of intravenous iron are of short duration and have small sample sizes. Large, randomised controlled studies with hard endpoints and long durations are needed to investigate the safety of these compounds.

Hepcidin production decreases in iron deficiency anaemia but increases in inflammatory states. Hepcidin could potentially be used to distinguish iron deficiency anaemia and anaemia of chronic disease. Because hepcidin assays are expensive and not routinely available, an algorithm to predict hepcidin concentrations has been proposed: transferrin saturation (%)–sTfR (mg/L)+C-reactive protein (mg/L).<sup>109</sup> Further studies might validate the diagnostic accuracy of hepcidin in iron deficiency anaemia.<sup>110</sup>

Hepcidin could also be a therapeutic target. Down-regulation could prevent retention of iron within the reticuloendothelial system. Different approaches targeting different regulatory steps have been tried to control hepcidin expression pharmacologically. They include hepcidin-sequestering agents (antibodies,

anticalins, and aptamers), inhibitors of the BMP/SMAD or IL6/STAT3 pathways, inhibitors of hepcidin transduction (small interfering or small hairpin RNA), or ferroportin stabilisers.<sup>111</sup> In a pilot study,<sup>112</sup> vitamin D supplementation was associated with a 34% decrease in circulating concentrations of hepcidin ( $p < 0.05$ ).<sup>112</sup> A fully human anti-hepcidin antibody affected iron metabolism in both mice and non-human primates,<sup>70</sup> and early phase clinical studies are beginning to be reported.<sup>113</sup>

#### Contributors

AL did the literature search. AL, ICM, and LP-B edited the paper and PC, ICM, and LP-B critically reviewed it.

#### Declaration of interests

AL declares no competing interests. PC has done consultancy for, served on advisory boards for, or received honoraria or speakers' fees from Abbvie, AstraZeneca, Bayer, Boehringer Ingelheim, Gilead, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Pfizer, Roche, Servier, and Vifor. He is an inventor of a patent application owned by his academic institution that is licensed to ILTOO, a biotechnology company developing low dose interleukin 2 in autoimmune diseases in which he holds shares. ICM has received speakers' fees and honoraria from AMAG, Vifor Pharma, Pharmacosmos, and Takeda; consulting fees from Amgen, Ortho Biotech, Roche, Bayer, Astellas, AstraZeneca, FibroGen; and research funding from AMAG, Vifor Pharma, Bayer, Astellas, and Noxxon. LP-B has received consulting fees from Merck, Abbott, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Shire, Therakos, Pharmacosmos, Pilège, BMS, UCB-pharma, Hospira, Celltrion, Takeda, Biogaran, Boehringer Ingelheim, Lilly, Pfizer, and HAC-Pharma, and lecture fees from Merck, Abbott, Takeda, Janssen, Ferring, Norgine, Tillots, Vifor, Therakos, and HAC-pharma.

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