

Iron deficiency

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Iron deficiency is one of the leading contributors to the global burden of disease, and particularly affects children, premenopausal women, and people in low-income and middle-income countries. Anaemia is one of many consequences of iron deficiency, and clinical and functional impairments can occur in the absence of anaemia. Iron deprivation from erythroblasts and other tissues occurs when total body stores of iron are low or when inflammation causes withholding of iron from the plasma, particularly through the action of hepcidin, the main regulator of systemic iron homeostasis. Oral iron therapy is the first line of treatment in most cases. Hepcidin upregulation by oral iron supplementation limits the absorption efficiency of high-dose oral iron supplementation, and of oral iron during inflammation. Modern parenteral iron formulations have substantially altered iron treatment and enable rapid, safe total-dose iron replacement. An underlying cause should be sought in all patients presenting with iron deficiency: screening for coeliac disease should be considered routinely, and endoscopic investigation to exclude bleeding gastrointestinal lesions is warranted in men and postmenopausal women presenting with iron deficiency anaemia. Iron supplementation programmes in low-income countries comprise part of the solution to meeting WHO Global Nutrition Targets.

Introduction

Iron deficiency (ID) and iron deficiency anaemia (IDA) cause an immense disease burden worldwide. Globally, there were over 1.2 billion cases of IDA in 2016.¹ IDA is among the five greatest causes of years lived with disability globally, the leading cause of years lived with disability in low-income and middle-income countries (LMICs), and is the leading cause of years lived with disability among women across 35 countries.¹ Controlling anaemia is a global health priority: WHO is aiming for a 50% reduction in anaemia prevalence in women by 2025.²

When iron intake is inadequate to meet requirements or to compensate for physiological or pathological losses, body iron stores become depleted. Absolute ID occurs when iron stores are insufficient to meet the needs of the individual, and is particularly common in young children (younger than 5 years) and premenopausal (especially pregnant) women. In patients with inflammation, withholding of iron from the plasma promotes iron deficient erythropoiesis and anaemia despite adequate body iron stores (functional iron deficiency). This process is common in patients with complex medical or surgical disorders, in people living in areas where infection prevalence is high, and in patients receiving erythropoiesis stimulating agents.³

Iron is crucial for numerous physiological and cellular processes, and ID causes diverse health consequences. Management of ID is an important and complex challenge faced by practitioners of medicine, nutrition, and public health worldwide. In this Seminar, we update the physiology, diagnosis, and clinical management of ID and identify future translational and clinical research directions.

Clinical presentation

ID can cause symptoms both in the presence and absence of anaemia, or can be asymptomatic. Common symptoms and signs include fatigue and lethargy,

reduced concentration, dizziness, tinnitus, pallor, and headache. In susceptible individuals, ID promotes restless leg syndrome.⁴ Other presentations include alopecia, dry hair or skin, koilonychia, and atrophic glossitis. Symptoms in infants (aged younger than 12 months) with ID can include poor feeding and irritability.⁵ Patients might also present with pica: the compulsive ingestion of non-nutritive foods, such as soil or clay, ice, or raw ingredients (eg, uncooked rice).⁶ ID and anaemia can also exacerbate symptoms and worsen the prognosis of medical conditions, including heart failure⁷ and ischaemic heart disease.⁸ Severe IDA can cause haemodynamic instability. Preoperative anaemia increases the risk of blood transfusion and is correlated with postoperative morbidity and mortality.⁹ Even when asymptomatic, ID can promote suboptimal functional

Search strategy and selection criteria

We searched MEDLINE, Embase, and the Cochrane Register, with combinations of the search terms including ("iron" OR "iron deficiency" OR "iron deficiency an[a]emia" OR "an[a]emia" OR "supplementation" OR "ferrous" OR "ferric" OR "ferric carboxymaltose" OR "iron carboxymaltose" OR "iron isomaltoside" OR "ferric derisomaltoside" OR "ferumoxytol" OR "iron sucrose" OR "iron polymaltose" OR "iron dextran" OR "nutrition" OR "iron absorption" OR "c[eliac disease]" OR "ferritin" OR "hepcidin" OR "ferroportin" OR "erythroferrone") AND ("public health" OR "epidemiology" OR "systematic review" OR "meta-analysis" OR "randomis[ed] controlled trial"). We searched from database inception until Dec 23, 2019. We also searched the reference lists of articles identified by this search strategy and selected the articles that we judged relevant. Where multiple sources of evidence were available for the same topic, we prioritised evidence from the most recently available systematic reviews or, where unavailable, studies using a randomised controlled trial design.

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outcomes, including impaired physical exercise performance, child neurocognitive development, and pregnancy outcomes.¹⁰

Epidemiology of ID

In 2016, 41·7% of children (younger than 5 years), 40·1% of pregnant women, and 32·5% of non-pregnant women were anaemic worldwide.^{11,12} WHO estimates that 42% of anaemia cases in children and 50% in women are amenable to iron supplementation, with variation between regions.¹³ Meta-analyses of population studies suggest the contribution of ID to anaemia could be smaller than the WHO estimate: 25% in children and 37% in women.¹⁴ Because of the paucity of population studies measuring iron biomarkers (beyond haemoglobin) and complexities in their interpretation during inflammation, prevalence estimates of ID in LMICs are uncertain. Representative population studies are possible: for example, the prevalence of ID in children aged 6 months to 5 years was estimated at 20·2% in Cameroon, 10·6% in Colombia, 18·4% in Laos, 26·1% in Liberia, and 14·8% in Mexico; in the same countries, the adjusted prevalence of ID in non-pregnant premenopausal women was 13·7%, 24·1%, 24·0%, 19·9%, and 30·4%, respectively.¹⁵ In the USA, 11% of children aged 6 months to 5 years, 15% of premenopausal women,¹⁵ and 18% of pregnant women¹⁶ have been estimated to have ID. ID and anaemia are more common in disadvantaged subpopulations, including people on low incomes, Indigenous peoples,¹⁷ and refugees and migrants from LMICs.¹⁸

Molecular pathology of ID

Most body iron is contained in haemoglobin found in erythrocytes (2500 mg), and much of the remaining iron is contained in myoglobin (130 mg) and enzymes (150 mg), with surplus iron stored in the liver; average iron stores the US population are 9·7 mg/kg in men, 5·7 mg/kg in premenopausal women, and 7·8 mg/kg in postmenopausal women.¹⁹ The 0·1% of total body iron contained in plasma is bound to transferrin, and in this form, iron can be supplied to tissues via binding to the transferrin receptor. At the cellular level, iron is crucial for numerous functions, including DNA synthesis and repair, enzymatic activity, mitochondrial function, and neurotransmitter production and function.²⁰ Plasma iron is rapidly turned over, and is predominantly sourced from iron scavenged from senescent red blood cells by macrophages, with a smaller amount (1–2 mg per day) absorbed from the diet at the duodenum, in which body iron acquisition is homeostatically regulated.⁶

Hepcidin, a liver-derived hormone, is the central regulator of systemic iron homeostasis (figure 1). Hepcidin binds to ferroportin, a protein that exports cellular iron, to block iron efflux by both occluding the channel and by inducing degradation of iron-loaded ferroportin.^{21,22} Inhibition of ferroportin-mediated iron efflux limits iron

export to the plasma, especially from macrophages and duodenal enterocytes, as well as hepatocytes. In response to both iron load and innate immune signalling, hepcidin is upregulated by the BMP/SMAD pathway and the IL-6-STAT3 pathway, respectively.²⁰ During absolute ID or periods of increased iron demand, hepcidin suppression upregulates iron absorption and recycling to optimise iron supply. During inflammation, increased concentrations of hepcidin and reduced ferroportin transcription²³ limits iron supply to the plasma, causing functional ID.

Reduced iron availability for red blood cell production causes iron deficient erythropoiesis manifesting as hypochromia, microcytosis, and eventually, anaemia. IDA affects erythropoiesis by influencing renal erythropoietin production and by modulating erythroblast EPO sensitivity, via TFR2.²⁴ In absolute ID, erythroblasts and erythrocytes donate iron via ferroportin, and can buffer plasma iron levels to mitigate serum iron depletion and protect erythrocytes from oxidative stress.^{25,26} These data reframe the assumption that microcytic anaemia is the main end-organ dysfunction from absolute ID; rather, erythroid cells release iron to maintain iron supply elsewhere.

Clinical pathophysiology of absolute ID

The main causes of absolute ID are excessive blood loss, and inadequate dietary iron intake or absorption that fails to meet physiological requirements (panel 1).

Blood loss

Each mL of blood contains 0·4–0·5 mg of iron.²⁷ Hence, negative iron balance is promoted by physiological, pathological, or iatrogenic blood losses.

Iron stores in premenopausal women are more greatly influenced by menstrual blood loss volume than dietary iron intake.²⁸ Heavy menstrual bleeding affects about 20% of women,²⁹ and ID affects around 50% of such cases in referral populations.³⁰ Up to 20% of women with heavy menstrual bleeding complicated by IDA have an underlying bleeding disorder (most often, von Willebrand disease).³¹

Gastrointestinal blood loss is the most important cause of ID in men and postmenopausal women. Gastrointestinal bleeding can be occult, in which case ID or IDA could be the only evidence of luminal pathology. Common upper gastrointestinal causes of bleeding include erosions or ulcers related to aspirin and other non-steroidal anti-inflammatory drugs, and peptic ulcer disease.^{32,33} The most important occult causes of lower gastrointestinal bleeding are colorectal cancer, angiodysplasia, and colonic polyps.^{32,33} In patients with IDA referred for endoscopy, potentially bleeding lesions were seen in 62%, including colorectal cancer in 11% and peptic ulceration in 19%.³² Even in male individuals younger than 50 years with IDA, colon cancer was seen in 0·8%.³⁴ A population study showed that, in the 2 years after a diagnosis of IDA and ID, the risk of gastrointestinal

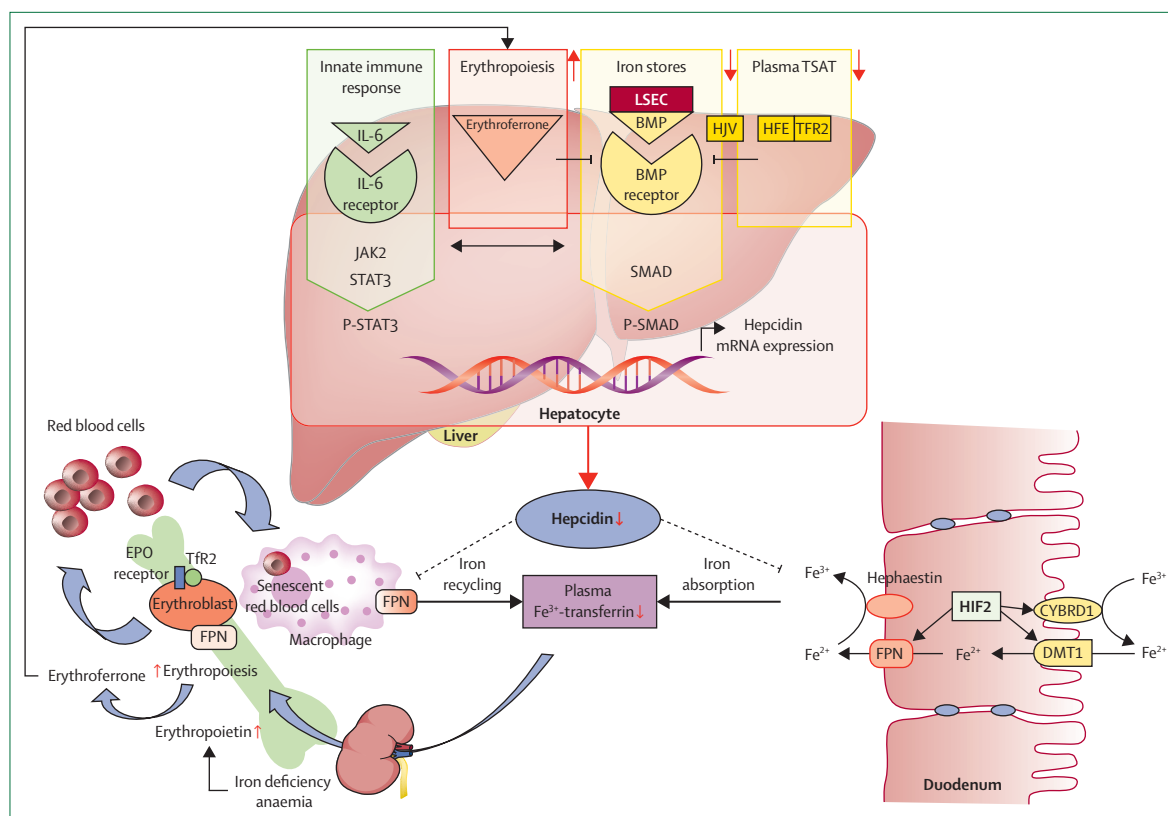


Figure 1: Coordinated homeostatic response to absolute and functional iron deficiency

Red arrows refer to physiological stimuli (eg, absolute iron deficiency or increased erythropoiesis) that suppress hepcidin expression. During absolute iron deficiency, decreased circulating transferrin saturation and liver iron storage suppress hepcidin transcription via reduced BMP-SMAD signalling (yellow pathway). As a consequence, duodenal and macrophage FPN proteins are stabilised, facilitating dietary iron absorption in duodenal enterocytes and release of iron from macrophages of the reticuloendothelial system, thereby increasing iron concentrations in the plasma. Additionally, reduced iron concentration in duodenal enterocytes is sensed by the iron-dependent prolyl hydroxylase domain enzymes that increase stability of the transcription factor HIF-2, which regulates transcription of apical (CYBRD1 and DMT1) and basolateral (FPN) iron transport machinery. During iron deficiency, in most cell types the IRP/IRE system stabilises mRNAs of proteins crucial for iron uptake (eg, TFR1 and DMT1) and suppresses the synthesis of proteins involved in the storage (ferritin), utilisation (cytoplasmic and mitochondrial iron-containing proteins), and export (FPN) of iron. In functional iron deficiency, inflammation increases hepatic hepcidin expression via IL6-JAK2-STAT3 signalling (green pathway), causing reduced FPN abundance and function on cells, depriving the plasma of iron. In response to iron deficiency anaemia, the kidney produces erythropoietin, which stimulates erythropoiesis. Erythroblast erythropoietin sensitivity can be modulated by TFR2. In absolute iron deficiency, erythroblasts and erythrocytes donate iron through FPN-mediated iron export. Increased erythropoiesis (eg, during recovery from anaemia) causes secretion of erythroferrone, which suppresses hepatic hepcidin expression via inhibition of BMP-SMAD signalling (red pathway). LSEC=liver sinusoidal endothelial cell. P=phosphorylated. TSAT=transferrin saturation.

malignancy is 6% in men and 1% in postmenopausal women, compared with 0.2% in non-anaemic, non-ID controls.³⁵ Contrastingly, in premenopausal women, no cases of cancer were diagnosed after IDA or ID. Other causes of gastrointestinal blood loss include inflammatory bowel disease; for example, 29% of patients with Crohn's disease and 17% with ulcerative colitis are anaemic,³⁶ with over 50% of such cases due to ID.³⁷ In LMICs, chronic hookworm infection promotes gastrointestinal blood loss, with the severity of ID proportional to the worm burden.³⁸

Each whole blood donation costs the donor about 250 mg of iron;³⁹ thus, whole blood donors have an increased risk of ID, with donation frequency being the predominant risk factor. A 2017 trial randomly assigned 45 263 whole blood donors to different inter-donation intervals; the prevalence of anaemia and ID at the shortest interval was 18% and 24% in men and 19%

and 27% in women, respectively, compared with 10% and 12% in men and 16% and 22% in women at the longest interval.⁴ Apheresis donation, in which red blood cells are returned to the donor, does not exacerbate ID.⁴⁰ Strategies to minimise ID in donors include predonation measurement of ferritin,⁴¹ prolonging the inter-donation interval, and providing postdonation iron supplementation.⁴²

Inadequate iron intake and absorption

The recommended daily intake for iron is highest in infants aged 7–12 months (11 mg), premenopausal women (18 mg), and during pregnancy (27 mg), and is lowest in adult men (8 mg).⁴³ Dietary iron occurs as haem iron in meat and non-haem iron from plant sources. Haem iron is efficiently absorbed and less susceptible to modulation by other dietary components, whereas absorption of non-haem iron is less efficient and susceptible to influence; for example, vitamin C enhances non-haem

Panel 1: Causes of absolute iron deficiency**Inadequate iron uptake**

- Inadequate nutritional iron intake
 - Inadequate dietary iron content
 - Low haem iron content (eg, from a vegetarian or vegan diet)
 - Food insecurity or low dietary diversity* (eg, resulting from poverty, especially in low-income countries)
 - Low iron content complementary diet* (eg, prolonged breastfeeding, or milk preference)
- Inadequate nutritional iron absorption
 - Concomitant consumption of inhibitors of iron absorption (eg, calcium or tea)
 - Inadequate stomach acidification
 - Atrophic gastritis
 - Use of antacids or proton pump inhibitors*
 - *Helicobacter pylori* infection
 - Procedures after gastric bypass
 - Intestinal mucosal dysfunction (eg, coeliac disease* or inflammatory bowel disease)
 - Obesity
 - Inappropriately increased hepcidin concentrations preventing iron absorption (eg, during chronic inflammation or iron-refractory iron deficiency anaemia caused by *TMPRSS6* mutations)

Increased iron requirements

- Growth (eg, during early childhood and adolescence)*
- Pregnancy*
- Physiological blood losses exceeding iron intake*
- Erythropoiesis stimulating agent therapy*

Blood loss

- Intestinal blood loss
 - Oesophageal
 - Varices
 - Carcinoma
 - Ulceration
 - Reflux oesophagitis
 - Gastric*
 - Gastric cancer and gastric polyps*
 - Gastric ulcers*
 - Use of aspirin and other non-steroidal anti-inflammatory drugs*
 - Angiodysplasia, telangiectasia, and gastric antral vascular ectasia (watermelon stomach)
 - Small bowel
 - Hookworm (*Ancylostoma duodenale* and *Necator americanus*)*
 - Inflammatory bowel disease*
 - Duodenal ulcers

- Lymphoma, cancer, and polyps
- Angiodysplasia, telangiectasia, and Meckel's diverticulum
- Extreme exercise-induced gastrointestinal bleeding
- Milk protein allergy (in infants younger than 12 months)
- Colon
 - Colon cancer*
 - Polyps*
 - Diverticular bleeding*
 - Angiodysplasia*
 - Inflammatory bowel disease*
 - Heyde's syndrome (severe aortic stenosis, acquired type 2 von Willebrand syndrome, angiodysplasia, and iron deficiency anaemia)
 - Hamartomatous polyps in Peutz-Jeghers syndrome
- Anal
 - Haemorrhoids
- Entire gastrointestinal tract
 - Hereditary haemorrhagic telangiectasia
- Gynaecological bleeding
 - Menstrual (eg, in premenopausal women and girls)*
 - Exacerbated by bleeding disorders (von Willebrand disease*, carrier for haemophilia A or B, and platelet dysfunction)
 - Use of an intrauterine device
 - Fibroids
 - Uterine or other reproductive tract cancers
- Urinary tract bleeding
 - Renal or bladder cancer
 - Urinary schistosomiasis (*Schistosoma haematobium*)
 - Intravascular haemolysis (eg, paroxysmal nocturnal haemoglobinuria)
 - Intravascular haemolysis (eg, valve haemolysis, march haemoglobinuria, and malaria)
- Respiratory bleeding
 - Severe haemoptysis (eg, lung cancer and infection)
- Blood donation (especially whole blood donation*)
- Excess iatrogenic blood losses (eg, excessive blood collection for diagnostic testing and iron losses during haemodialysis)
- Self-inflicted blood loss (Munchausen syndrome)

Exercise

- Multifactorial: reduced dietary iron intake, reduced iron absorption due to inflammation, increased losses in sweat, gastrointestinal bleeding, and haemolysis with haemoglobinuria

*Common important causes to consider in primary care.

iron absorption, and phytates (found in seeds and grains), calcium, and tannins (found in tea and coffee) inhibit non-haem iron absorption.⁴⁴ Iron absorption from vegetarian diets is less efficient than meat inclusive diets,

and vegetarians have lower iron stores and are more likely to be iron deficient.⁴⁵ A systematic review showed that adult vegetarians have reduced serum ferritin levels compared with non-vegetarians ($-29.7 \mu\text{g/L}$ in vegetarians

[95% CI -39.7 to -19.7]), with the effects more pronounced in men (-61.9 µg/L [-85.6 to -38.2]) than in women (-13.5 µg/L [-23.0 to -4.0]).⁴⁵

Gastric acidity is crucial for maintaining iron solubility in the duodenum for absorption. Patients using proton pump inhibitors or histamine-2 receptor antagonists are at a dose-dependent and duration-dependent increased risk of ID.⁴⁶ ID develops in 20% of patients after gastrectomy (for cancer) or gastric bypass surgery (for obesity). Autoimmune gastritis, an inflammatory condition characterised by autoantibodies against gastric parietal cells and intrinsic factor, causes cobalamin deficiency and megaloblastic anaemia and was reported in 27% of patients with otherwise unexplained IDA.⁴⁷ *Helicobacter pylori* was estimated to have infected 4.4 billion people worldwide in 2015, with the prevalence highest in poorest populations.⁴⁸ A meta-analysis reported an association between *H. pylori* and IDA and ID, and evidence that eradication could improve iron stores.⁴⁹

Coeliac disease is a chronic small intestinal immune-mediated enteropathy precipitated in genetically predisposed individuals by exposure to dietary gluten, a protein in wheat, barley, and rye.^{50,51} Strict removal of dietary gluten promotes mucosal healing. The global seroprevalence is 1.4% and the prevalence confirmed by biopsy is 0.7%.⁵² ID and IDA in coeliac disease can occur in the absence of other malabsorptive manifestations and might be the presenting feature. One in 31 patients with IDA could have coeliac disease,⁵³ with this risk unaffected by sex, age, or prevalence of coeliac disease in the underlying population, indicating coeliac disease is a consistent risk factor for IDA.

Iron absorption in women who are overweight and obese is lower than in women in the healthy weight range⁵⁴ due to increased hepcidin concentrations.⁵⁵ A systematic review showed that, compared with people who were a healthy weight, individuals who were overweight and obese had lower transferrin saturation (-2.34% [95% CI -3.29 to -1.40]) and a higher risk of developing ID (odds ratio [OR] 1.31 [1.01-1.68]).⁵⁶

Patients with mutations in the *TMPRSS6* gene have iron-refractory IDA, a rare autosomal recessive disease hallmarked by the inability to absorb dietary iron due to increased hepcidin concentrations that block iron release from macrophages and duodenal enterocytes.⁵⁷ Genome-wide association studies have showed that, in the general population, *TMPRSS6* polymorphisms influence haemoglobin concentration, red blood cell size, and iron stores,⁵⁸ which implies a genetic susceptibility to ID.

Absolute and functional ID can exist independently or in combination to cause anaemia (figure 2). Systemic inflammation increases hepcidin concentrations, which impairs iron absorption. For example, women in Côte d'Ivoire with asymptomatic *Plasmodium falciparum* parasitaemia showed improved iron absorption after receiving antimalarials.⁵⁹ In The Gambia, chronic low

levels of systemic inflammation in young children (aged 6-23 months) have been shown to increase hepcidin concentrations and impair iron absorption, potentially contributing to IDA prevalence.⁶⁰ Patients with chronic inflammatory conditions can experience similar pathophysiology.⁶¹

Increased iron needs during life

For the first 6 months of life, babies predominantly meet iron needs from their birth iron endowment,⁶² which is influenced by birthweight, gestation duration, and the timing of cord clamping. Babies who are preterm, small for their gestational age, and of low birthweight have lower iron stores⁶³ and are at an increased risk of ID. Delaying cord clamping for 1-3 min allows neonates to maximally retain red blood cells.⁶⁴ During the second 6 months of life, iron stores are influenced by birth endowments, by use from growth,⁶⁵ and by nutritional iron content.⁶⁶

During pregnancy, iron needs markedly increase from the second trimester⁶⁷ to support the 30% expansion of the red blood cell mass (which requires about 450 mg iron in a woman weighing 55 kg), although plasma volume expansion promotes physiological anaemia with a haemoglobin concentration nadir mid-second trimester.⁶⁸ Furthermore, the fetus requires about 270 mg iron, which is mostly accreted in the third trimester. During childbirth, about 150 mg iron is lost from bleeding. To meet needs, intestinal iron absorption increases as much as nine times from early to late pregnancy, normalising in the postpartum period.⁶⁹ This increased iron absorption is accomplished because of hepcidin suppression early in the second trimester.⁷⁰ Hepcidin suppression is also crucial for placental iron transfer during the third trimester.⁷¹ Recycling of iron from the expanded red blood cell pool after pregnancy together with amenorrhoea reduces the net pregnancy iron requirement to about 580 mg.⁶⁷ Despite homeostatic compensations, many women are unable to meet their pregnancy iron requirements, especially if they enter pregnancy with diminished stores.

ID affects up to 35% of female individuals and 11% of male individuals who are elite (especially endurance) athletes. The pathophysiology is multifactorial and includes interactions between impaired nutritional iron absorption due to inflammation, exercise-induced gastrointestinal bleeding, heavy menstrual bleeding, iron losses in sweat, and increased requirements for erythropoiesis.^{72,73}

Diagnosis of ID

The gold standard test for absolute ID is the finding of absent stainable bone marrow iron. Patients with functional ID have detectable stainable bone marrow iron unless they have concomitant absolute ID (figure 2). Bone marrow aspiration is invasive and rarely done routinely for diagnosis of ID, but it remains useful in complex cases. ID is usually diagnosed by blood biomarkers (figure 3). A full

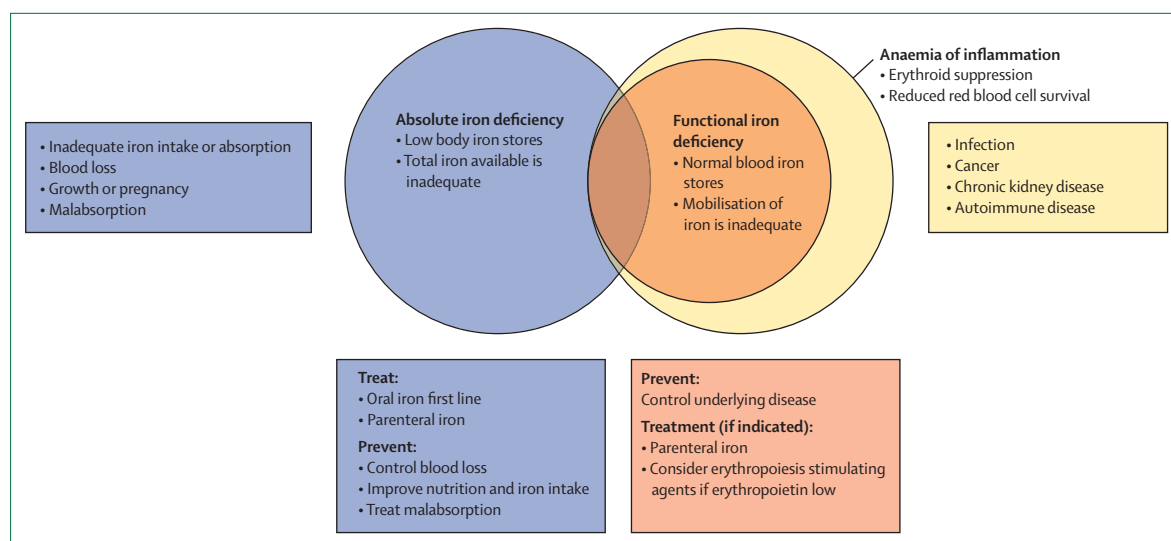


Figure 2: Absolute and functional iron deficiency

In absolute iron deficiency, total body iron concentrations are reduced due to uncompensated negative iron balance. Patients with absolute iron deficiency have low tissue iron stores, low bone marrow iron stores, and low plasma iron (transferrin saturation), and in the absence of other signals, hepcidin is suppressed, homeostatically upregulating iron absorption. Anaemia of inflammation is common in patients with conditions including acute and chronic infection, autoimmune conditions, cancer, recent surgery, and heart failure. The predominant mechanism of anaemia of inflammation is functional iron deficiency, in which inflammation-mediated increases in hepcidin prevent cellular iron export (especially from macrophages) to the plasma, resulting in reduced transferrin saturation, iron deficient erythropoiesis, and anaemia, even with sufficient body iron stores. Functional iron deficiency is the predominant mechanism of anaemia of inflammation, but other causes (eg, direct bone marrow suppression, reduced erythropoietin production and marrow responsiveness, and reduced red blood cell survival) can also contribute. Functional and absolute iron deficiency can coexist, and functional iron deficiency might promote absolute iron deficiency through sustained impairment of iron uptake. Therapy for absolute iron deficiency focuses on improving iron stores, ameliorating blood losses, and optimising iron absorption. Therapy for functional iron deficiency focuses on controlling the underlying conditions. Parenteral iron therapy can be used if the patient is symptomatically anaemic.

blood count with film can indicate anaemia, microcytic, hypochromic red blood cells with an increased red blood cell distribution width (anisocytosis), and elongated (pencil shaped) cells.

Serum (or plasma) ferritin is the mainstay for ID diagnosis.⁷⁴ Little primary evidence is available from high quality studies to justify specific thresholds. In a study of 238 healthy women, a ferritin threshold of less than 15 µg/L predicted absent bone marrow iron stores with a sensitivity of 75% and specificity of 98%, and a threshold of 30 µg/L improved sensitivity to 93% at the expense of specificity (75%).⁷⁵ Less than 15 µg/L ferritin is specific for ID,⁷⁶ whereas less than 30 µg/L ferritin coupled with a high pretest probability is highly suggestive. Use of lower ferritin thresholds for ID diagnosis in children (eg, less than 12 µg/L) or different thresholds between women and men is not evidence-based. Because ferritin is a positive acute phase protein, diagnosis of ID can be obscured by inflammation.^{77,78} Strategies for adjusting ferritin concentrations in inflammation include developing a regression equation on the basis of the correlation between ferritin and inflammatory markers, or in the presence of inflammation, inflating the ferritin threshold.⁷⁹ When inflammation is present, WHO defines ID at a ferritin concentration less than 30 µg/L in children under 5 years and less than 70 µg/L in older children and adults.⁷⁶ Diagnosing absolute ID in patients with inflammation is important for identifying

underlying factors (such as bleeding) and for population estimates of ID; however, treatment approaches should consider coexistent functional ID (figure 2). As with inflammation, ferritin concentrations are also increased in liver disease, including non-alcoholic fatty liver disease, and epidemiological data suggest that population ferritin concentrations are increasing with increasing rates of obesity.⁸⁰

Serum iron concentration is reduced in both ID and inflammation; alone its concentrations do not indicate ID. Transferrin saturation (eg, less than 20%) is useful to define low plasma iron availability to tissues in both absolute and functional ID. Soluble transferrin receptor (sTfR) is a useful index of tissue iron needs, and the sTfR:log(ferritin) ratio has useful predictive value for bone marrow iron stores, especially in patients with inflammation.⁸¹ sTfR is also a biomarker of erythropoiesis. Its drawback is scarce clinical availability and different thresholds between assays due to the fact that different sTfR tests have not been formally standardised.

Reticulocyte haemoglobin content, hypochromic red blood cell percentage, and related indices can be measured on several modern automated haematology analysers. The percentage of hypochromic red blood cells reflects iron restricted erythropoiesis during the preceding 2–3 months.⁸² Reticulocyte haemoglobin content reflects iron availability for erythropoiesis of the

| | Iron repletion | Low iron stores | Absolute iron deficiency (non-anaemic) | Absolute iron deficiency (anaemia) | Functional iron deficiency | Functional iron deficiency with absolute iron deficiency | Iron-refractory iron deficiency anaemia due to <i>TMPRSS6</i> variants |
|--|--|--|---|---|--|--|--|
| Body iron stores | Body iron stores and iron available for erythropoiesis | | | | Body iron stores | | |
| | | | | | Iron available for erythropoiesis | | Body iron stores and iron available for erythropoiesis |
| No systemic inflammation | | | | | Systemic inflammation | | No systemic inflammation |
| Symptoms | Nil | Asymptomatic or mildly symptomatic (eg, fatigue); possible reduced physical or cognitive function; underlying condition could be evident (eg, bleeding or nutrition) | Asymptomatic or symptomatic: fatigue, poor concentration, dizziness, tinnitus, headache, pica, or restless legs | Likely symptomatic, decompensation if severe or poor medical reserves | Symptoms of underlying condition; symptoms of anaemia | Symptoms of underlying condition; symptoms of anaemia | Symptomatic iron deficiency anaemia |
| Haemoglobin | Normal | Normal | Normal or low-normal | Reduced (anaemic) | Mild to moderate anaemia | Mild to moderate anaemia | Reduced (anaemic) |
| Mean cell volume and mean cell haemoglobin concentration | Normal | Normal | Normal or reduced | Reduced | Normal or mild reduction | Reduced | Reduced |
| Ferritin | >30–60 µg/L | 15–30 µg/L | <15–30 µg/L | <15–30 µg/L | Normal or increased depending on inflammation and body iron stores | <70–100 µg/L depending on degree of inflammation | Typically 20–50 µg/L |
| Transferrin saturation | >20% | Usually >20% | <20% | <15% | Usually <20% | <20% | <20%, usually <5% |
| Reticulocyte haemoglobin content* | Normal | Normal | Low | Low | Low | Low | Low |
| Soluble transferrin receptor* | Normal | Normal | Increased | Increased | Normal | Normal or increased | Increased |
| Hepcidin* | Normal | Low-normal | Low | Very low | Increased relative to transferrin saturation | Normal or reduced | High relative to transferrin saturation |
| Bone marrow stainable iron | Normal | Detectable or absent | Absent | Absent | Detectable | Absent | Absent or trace |

Figure 3: Biomarkers for diagnosis of iron deficiency

Suggested interpretation of both widely available and emerging biomarkers to diagnose different iron deficiency syndromes. Concomitant measurement of an inflammatory biomarker (eg, C-reactive protein) is recommended to enable interpretation of ferritin in patients at risk of inflammation. *Diagnostic thresholds for reticulocyte haemoglobin content vary between type of analyser, and for non-standardised hepcidin and soluble transferrin receptor assays, between manufacturers.

previous 3–4 days before testing.⁸³ Both parameters are useful for detecting iron restricted erythropoiesis due to absolute or functional ID, or recovery in response to therapy.⁸⁴ The use of these novel red blood cell parameters is constrained by the absence of universal clinical decision limits. Finally, an increase in haemoglobin concentration after a trial of iron indicates baseline ID.

Measurement of hepcidin concentration is emerging as a test for ID and for distinguishing absolute from functional ID.⁸⁵ Hepcidin concentration has been studied in pregnant and non-pregnant women, in

children, and in patients with rheumatoid arthritis, inflammatory bowel disease, cancer-related anaemia, or critical illness.^{86–88} Suppressed concentrations indicate physiological iron need, predict responsiveness to iron, and can enable personalisation of the route of iron replenishment.⁸⁹ Measurement of hepcidin is mostly limited to research settings but is offered clinically by some European hospital laboratories. The use of calibration materials commutable with human plasma or serum will allow standardisation that is essential to enable routine clinical hepcidin testing.⁹⁰

Further investigation of ID

ID is the presenting manifestation of various pathophysiological processes, and investigation to exclude serious pathology and define the underlying cause is essential. The nature and extent of testing depends on the patient demographic (appendix p 1).

See Online for appendix

Coeliac serological testing should be considered in patients with non-anaemic ID and is recommended for all patients with IDA.^{33,91} Measurement of tissue transglutaminase IgA antibodies is the preferred test, and should be combined with IgA concentrations or an IgG-based assay, such as DGP, because 2–3% of patients with coeliac disease are IgA deficient. Anti-endomysial antibodies are highly specific for coeliac disease. If serological tests are positive, coeliac disease should be confirmed by small intestinal evaluation.⁹¹

Men and postmenopausal women with IDA are at high risk of bleeding gastrointestinal lesions and should be considered for upper and lower gastrointestinal endoscopy.^{33,92} A decision to defer endoscopic investigation in patients with identifiable non-gastrointestinal blood losses should only be made after careful consideration of risks and benefits. Premenopausal women with IDA should be considered for endoscopy if they have symptoms of gastrointestinal disease (eg, altered bowel habit or overt bleeding), a personal history or a first-degree relative with a history of colorectal cancer, or if they do not have a clear explanation for ID, such as ongoing menstrual blood loss.³³ The diagnostic yield from endoscopic procedures in the asymptomatic premenopausal patient population is unclear.⁹² Faecal occult blood testing should not be used to target endoscopy in patients with ID. CT colonography can be considered when colonoscopy is contraindicated but does not have the sensitivity for smaller mucosal lesions (less than 6 mm) and does not permit biopsy or polypectomy. Endoscopy is not recommended as routine in patients with non-anaemic ID unless there are other concerns for gastrointestinal malignancy, or if ID is recurrent.³³

If upper and lower endoscopic studies exclude substantial pathology, it is reasonable to withhold further gastrointestinal investigation unless there is recurrent, refractory, or severe IDA.³³ Small intestinal investigation can be accomplished by video capsule endoscopy (a non-invasive imaging approach) or enteroscopy (an endoscopic approach enabling tissue sampling and therapeutic manoeuvres). Finally, assessment for autoimmune gastritis and *H pylori* should be considered in all patients with ID or IDA for whom no other underlying cause has been diagnosed.⁴⁷

Treatment of ID

A holistic approach to clinical management of ID is outlined in the appendix (p 2). The aim of treatment is to replenish iron stores and normalise haemoglobin concentrations if anaemia is present. Indications for therapy in ID include anaemia, symptoms, crucial periods

that risk impaired outcomes (eg, pregnancy or before surgery), and when progression is likely to be due to uncorrected underlying factors; for example, ongoing growth in children, poor iron intake, or blood losses. Most patients with non-anaemic ID who are seen clinically will have presented with symptoms and should be treated, whereas patients who are entirely asymptomatic should probably still receive some intervention to prevent further decline in iron stores.

Oral iron supplementation

Many oral iron products with varying doses and formulations are available. Oral iron formulations include ferrous salts (eg, ferrous sulphate) as well as other agents, including iron polymaltose. Dosing is based on the elemental iron content (eg, 325 mg ferrous sulphate contains 105 mg elemental iron). The use of ferrous salts for iron therapy is limited by gastrointestinal adverse events. A systematic review of placebo-controlled trials supported that ferrous salts increased gastrointestinal symptoms (OR 2.32 [95% CI 1.74–3.08]); particularly constipation (12%), nausea (11%), and diarrhoea (8%).⁹³ Gastrointestinal symptoms limit adherence and cause cessation of therapy.⁹⁴ Slow-release iron formulations aim to reduce side-effects; however, this type of formulation is not effective in clinical studies.⁹³

Historically, doses of elemental iron as high as 100–200 mg per day across two to three divided doses were recommended.⁹⁵ However, stable isotope studies have redefined optimal oral regimens. In women who are iron deficient and non-anaemic, elemental iron doses of 60 mg or greater raise the concentration of hepcidin for 24 h, blocking absorption of subsequent doses; as iron doses increase, fractional absorption from subsequent doses declines, such that over a six times increase in dose absolute absorption increases by only three times.⁹⁶ When sustained absorption of elemental iron from twice daily, daily, and alternate daily dosing was measured, 33% more iron was absorbed over 14 doses when given alternate daily compared with daily; dividing doses worsened fractional absorption.⁹⁷ In women with mild IDA, fractional iron absorption was higher when iron was given on alternate days compared with consecutive days, and higher from 100 mg doses compared with 200 mg doses.⁹⁸ This approach to iron therapy was tested in a small randomised controlled trial (RCT) comparing treatment of IDA with alternate day dosing at 120 mg with 60 mg twice daily dosing.⁹⁹ Patients receiving twice daily dosing had faster increases in haemoglobin concentration, but patients receiving alternate day dosing had similar increments once they had received the same total amount of iron, and experienced fewer gastrointestinal adverse events. Larger studies will be needed to define the comparative effectiveness of treatment regimens for alternate day dosing. Together, these studies^{96–98} suggest optimal regimens of oral iron dosing. High doses of iron, and dividing doses twice or thrice daily, is physiologically

inefficient; instead, iron absorption is most efficient with intermediate doses and on alternate days, and this approach is recommended in patients with mild symptoms, or no or mild anaemia. However, high doses do increase absolute absorption; therefore, higher doses can be considered when iron deficits are severe.

Novel oral therapies are emerging that combine ferric iron with carriers to optimise absorption and reduce adverse gastrointestinal effects. Ferric maltol is approved in Europe and in the USA for treatment of IDA in adults.¹⁰⁰ Sucrosomial iron has been evaluated in IDA in patients with kidney disease, cancer, and inflammatory bowel disease, and during pregnancy.¹⁰¹ Iron hydroxide adipate tartrate is being trialled for prevention and treatment of IDA in young African children (aged 6–35 months).¹⁰²

Parenteral iron therapy

New generation parenteral iron preparations have revolutionised therapy for ID. Intravenous preparations comprise an iron core encapsulated in a carbohydrate shell to delay iron release.¹⁰³ The maximum single infusion dose depends on the stability of the shell. Iron sucrose has a less stable shell, limiting dosing to about 200 mg per infusion.¹⁰³ Ferric carboxymaltose, ferric derisomaltose, and ferumoxytol have stable shells, slowing iron release and allowing higher doses of iron to be delivered in single infusions, thereby minimising the number of clinical contacts.

Safety of parenteral iron is a historical concern, based on experience from obsolete high molecular weight iron dextran formulations. A systematic review of 97 RCTs across various (non-high molecular weight dextran) parenteral formulations showed that parenteral iron was not associated with serious adverse events (relative risk [RR] 1.04 [95% CI 0.93–1.17]),¹⁰⁴ nor were ferric carboxymaltose, iron sucrose, ferric derisomaltose, or ferumoxytol associated with serious infusion reactions; milder reactions, such as urticaria, and delayed effects, including headache and arthralgias, were not uncommon. Nonetheless, regulators still advise that parenteral iron should only be given when equipment and staff for management of hypersensitivity reactions are available, and that patients are monitored for hypersensitivity during infusion and for 30 min thereafter.¹⁰⁵ Parenteral iron formulations are now widely used in outpatient settings and primary care. A systematic review did not identify increased risk of infection from parenteral iron.¹⁰⁴ However, given that iron can promote microbial growth, parenteral iron should be avoided in patients with active sepsis. An underappreciated clinical and medico-legal risk of parenteral iron is skin staining if extravasation occurs, and patients should be counselled of this risk.¹⁰⁶ Purchase price of the new drugs are expensive compared with iron sucrose and oral iron; these costs might be offset by the shorter infusion times and fewer clinic visits needed for total dose replacement.¹⁰⁷

Ferric carboxymaltose has been available for over a decade, is currently marketed in over 50 countries,¹⁰⁸ and has been tested across a range of clinical indications. A dose of 15–20 mg/kg up to 1000 mg (750 mg in the USA) diluted in 250 mL saline is conventionally administered in a 15 min infusion. Biochemical hypophosphataemia is common after administration of ferric carboxymaltose,¹⁰⁹ and is due to a drug-induced increase in FGF23 concentration that acts on the renal tubules to induce phosphaturia.¹¹⁰ Hypophosphataemia is generally transient, recovering over 8–10 weeks. Although most cases seem asymptomatic,¹¹¹ severe clinical hypophosphataemia has been reported,¹¹² and patients receiving recurrent doses of ferric carboxymaltose can develop osteomalacia.¹¹³ Routine phosphate measurement and replacement after ferric carboxymaltose is not usually necessary, but clinicians should consider hypophosphataemia in patients presenting with muscle dysfunction or changes in mental state in the weeks after treatment and in patients with bone pain or fractures after recurrent usage.

Ferumoxytol is available in the USA: up to 510 mg iron can be delivered in a single dose, which must be diluted in saline or glucose and given over 15 min.¹¹⁴ Off-label administration of 1020 mg as a single 30-min infusion has been reported.¹¹⁵ A trial comparing ferumoxytol with ferric carboxymaltose showed similar adverse event profiles, similar efficacy, and lower risks of hypophosphataemia from ferumoxytol¹⁰⁹ due to blunted increases in FGF23.¹¹⁰ Ferric derisomaltose is available in Europe and has recently been licensed in the USA and Australia. This treatment enables doses of 1500 mg to be delivered over a 30 min infusion, making it an attractive option in patients who are profoundly iron deficient. Twin RCTs showed that biochemical hypophosphataemia is less common with ferric derisomaltose than ferric carboxymaltose (around 8% vs around 74%).¹¹⁶ Low molecular weight iron dextran is a cheap iron formulation available in the USA which allows total-dose iron replacement over about 60 min.¹¹⁷ In Australia and New Zealand, iron polymaltose has long been available as a parenteral formulation, is cheap, and can deliver high doses (up to 2000 mg) over 60–120 min infusions.¹¹⁸

In pregnancy, the use of parenteral iron is restricted to the second and third trimesters.¹¹⁹ Case series have reported safe and efficacious use of parenteral iron in children aged 9 months to 18 years for treatment indications similar to adults.¹²⁰

Clinical benefits of iron therapy

Oral iron is the first line of treatment in uncomplicated ID, but the threshold for use of parenteral iron in cases of moderate or severe anaemia, severe clinical symptoms, poor response, intolerable adverse effects, or difficult adherence is lowering. Parenteral iron generally promotes superior haemoglobin improvements: for example, a systematic review of 13 RCTs showed parenteral iron produces a 5.3 g/L (95% CI 2.1–7.5) greater increase in

haemoglobin compared with oral iron.¹²¹ Considerations for choosing between oral and parenteral iron are discussed in this Seminar and summarised in the appendix (p 2).

Iron interventions in patients without complex medical conditions

Iron supplementation inevitably increases haemoglobin and ferritin.^{122–125} Clinically, iron in adults with non-anaemic ID reduces self-reported fatigue (standardised mean difference [MD] -0.38 [95% CI -0.52 to -0.23]).¹²⁶ Trials of iron in asymptomatic (non-fatigued) women with ID have shown that iron does not generally improve fatigue scores, suggesting that iron benefits patients with ID who present symptomatically but not patients with ID who are asymptomatic. Iron can improve exercise performance: a systematic review showed that, in women with ID, oral iron improved maximal exercise performance (VO_2 max by 2.35 mL/kg per min [95% CI 0.82 – 3.88]) and submaximal performance (heart rate 4.05 beats per min lower [0.85–7.25]).¹²⁷ Parenteral iron did not improve VO_2 max in elite athletes.¹²⁸ A systematic review showed that iron (both oral and parenteral) reduced International Restless Legs Syndrome scores (MD -3.55 [95% CI -5.41 to -1.68]).¹²⁹ Meta-analyses have shown that iron improves cognitive performance in children aged 5–12 years but evidence is minimal for benefits on cognitive development in children younger than 5 years, and especially in children younger than 2 years.^{124,125}

A 2015 Cochrane review evaluating antenatal iron supplementation showed that iron reduced anaemia at term by 70%; in a subgroup analysis in which anaemic participants were not specifically excluded, antenatal iron reduced the risk of low birthweight (RR 0.82 [95% CI 0.72 – 0.94]) and increased birthweight by 33.02 g (95% CI 3.65 – 62.38).¹²³ An RCT in Kenya compared oral iron with placebo in 470 unselected pregnant women and had 100% adherence: babies of mothers randomly assigned to iron were 150 g heavier and born on average 3.4 days later than those born to mothers receiving placebo. Importantly, benefits on birthweight were unrelated to baseline anaemia status but were only noted in women with initial ID (in whom there was a 234 g increase in birthweight of the babies).¹³⁰ Systematic reviews summarising RCTs comparing parenteral with oral iron in pregnancy^{131,132} each found parenteral iron superior for improvements in haemoglobin (MD 7.4 g/L [95% CI 3.9 – 11.0]);¹³² furthermore, parenteral iron produced a small but significant increase in birthweight (about 58 g),^{131,132} and could reduce maternal transfusion needs (OR 0.19 [95% CI 0.05 – 0.78]).¹³² Collectively, these data emphasise the crucial importance of screening for, preventing, and treating, ID during pregnancy, affirm the importance of routine oral iron supplementation in settings where the risk of antenatal anaemia is likely high,¹³³ and establish a role for parenteral iron in women with

moderate or severe IDA beyond the first trimester, especially in the third trimester when fetal iron transfer is highest and delivery (and risk of blood loss) is imminent.^{119,134}

In the postpartum period, a systematic review found that, compared with oral iron, women treated with intravenous iron had a haemoglobin concentration 8.8 g/L [95% CI 4.1 – 13.5] higher, with superiority seen as early as 1 week postinfusion.¹³⁵

Parenteral iron in patients with complex conditions

Impaired oral iron use in functional ID can be circumvented by parenteral iron. Parenteral iron should be considered in the first line of treatment for functional ID, including for patients with the following complex conditions.

Congestive cardiac failure

Anaemia and functional ID are common in patients with chronic systolic heart failure. Single-dose¹³⁶ and sustained¹³⁷ treatment with ferric carboxymaltose improves exercise capacity and quality of life in patients with chronic New York Heart Association Class II or III systolic heart failure and a serum ferritin concentration less than 100 µg/L or a ferritin concentration between 100 µg/L and 299 µg/L with a transferrin saturation less than 20%. A systematic review showed that patients with heart failure receiving parenteral iron (as ferric carboxymaltose or iron sucrose) showed reduced death and heart failure on hospital admission (OR 0.47 [95% CI 0.32 – 0.69]), and improved symptoms, 6 min walk test distance, and left ventricular ejection fraction, and reduced N-terminal pro-hormone B-type natriuretic peptide.¹³⁸ Conversely, oral iron supplementation does not benefit cardiac endpoints in patients with systolic heart failure.¹³⁹ Finally, a multicentre RCT of patients admitted to hospital with acute heart failure and reduced ejection fraction and reduced serum ferritin or transferrin saturation (serum ferritin concentration less than 100 µg/L or a ferritin concentration between 100 µg/L and 299 µg/L with a transferrin saturation less than 20%) reported that ferric carboxymaltose at discharge and 6 weeks after discharge, with maintenance as needed thereafter, reduced heart failure-associated hospital admissions compared with placebo.¹⁴⁰ European Society of Cardiology guidelines recommend that ferric carboxymaltose should be considered in symptomatic patients with low ferritin or transferrin saturation to improve heart failure symptoms, exercise capacity, and quality of life.¹⁴¹

Inflammatory bowel disease

Parenteral iron is preferred in patients with inflammatory bowel disease and moderate to severe anaemia, with active disease, or for whom oral iron is not tolerated or ineffective. A systematic review showed that parenteral iron was more effective at promoting improvements of

20 g/L or higher in haemoglobin concentration compared with oral iron (OR 1.57 [95% CI 1.13–2.18]), with a lower rate of treatment discontinuation due to adverse events.¹⁴²

Perioperative optimisation

Preoperative anaemia is associated with increased risk of in-hospital (OR 2.09 [95% CI 1.48–2.95]) and 30-day postoperative (OR 2.20 [1.68–2.88]) mortality, along with other serious adverse events.¹⁴³ Preoperative therapy with iron improves haemoglobin concentrations,¹⁴⁴ although effects on transfusion requirements also relate to broader operative and postoperative aspects of blood management for patients. A systematic review suggested that preoperative iron supplementation (oral or intravenous) reduces transfusion (RR 0.47 [95% CI 0.28–0.79]);¹⁴³ however, a large RCT of patients with anaemia (but not necessarily with ID) undergoing major abdominal surgery did not find a reduction in transfusion needs from preoperative treatment with ferric carboxymaltose, although hospital readmissions were significantly reduced in the ferric carboxymaltose arm, especially in the first 8 weeks postoperatively.¹⁴⁵ Screening for anaemia and defining the contribution of ID should be undertaken before elective surgery, and IDA should be treated with iron replacement, with the selection of route dependent on the severity of the anaemia, the patient's ability to absorb oral iron, and the time until surgery (parenteral iron is preferred if operation is within 6 weeks from diagnosis of ID).^{143,146}

Postoperative anaemia is common due to blood losses during surgery and diagnostic testing, and functional ID, or can be spurious due to intraoperative or postoperative haemodilution. Parenteral iron is superior to placebo¹⁴⁷ and oral iron¹⁴⁸ in restoring haemoglobin concentrations in patients with postoperative anaemia after a variety of procedures, although effects on non-haematological clinical endpoints are uncertain.¹⁴⁹

Chronic kidney disease

Compared with oral iron, parenteral iron produces higher haemoglobin concentrations (MD 7.2 g/L [95% CI 0.39–1.05]), increases the likelihood a patient will reach their target haemoglobin concentration (RR 1.71 [95% CI 1.43–2.04]), and reduces the required dose of erythropoiesis stimulating agents in chronic kidney disease.¹⁵⁰ A large RCT (n=2141) showed that, compared with reactive treatment with parenteral iron to keep ferritin above 200 µg/L, administering regular, high doses of intravenous iron (eg, 400 mg iron sucrose monthly, unless ferritin exceeded 700 µg/L) improved mortality and morbidity from cardiovascular events and permitted reduced dosing of erythropoiesis stimulating agents.¹⁵¹ Because ferric carboxymaltose-induced hypophosphataemia is due to renal losses, it is less common in chronic kidney disease.

An emerging non-parenteral approach for treatment of ID in chronic kidney disease is oral ferric citrate, an

intestinal phosphate binder that can improve iron stores and reduce anaemia (even when therapy with parenteral iron and erythropoietin stimulating agents is suspended) while controlling hyperphosphataemia in patients who are dialysis dependent¹⁵² and those who are non-dialysis dependent.¹⁵³

Preventing ID in LMICs

At the population level, ID and IDA is an outcome of social, environmental, and nutritional determinants that converge to constrain iron intake, increase iron demands, cause blood loss due to helminth infection, and limit iron absorption and use due to inflammation.¹⁵⁴ WHO recommends population level interventions to prevent ID,¹⁵⁵ including central fortification with iron of staple foods and condiments; home fortification of infant complementary foods with iron and other micronutrients; and daily or weekly iron supplementation during childhood, adolescence, and pregnancy, and in non-pregnant

Panel 2: Future research and clinical directions

Epidemiology

- Improved data on prevalence of iron deficiency across low-income, middle-income, and high-income countries through routine incorporation of iron biomarkers in population surveys will enable appropriate targeting of public health and clinical interventions

Diagnosis

- Rational, evidence-based thresholds for defining iron deficiency using existing biomarkers, such as ferritin and standardised soluble transferrin receptor, and available but underused biomarkers, such as reticulocyte haemoglobin content
- Identification and validation of functional markers of iron deficiency beyond haemoglobin
- Introduction of standardised hepcidin measurement into routine clinical diagnosis through availability on automated laboratory platforms
- Non-invasive faecal and blood-based tools and improved imaging technology to detect luminal pathology, such as malignancy and coeliac disease

Treatment

- Further characterisation of the clinical role and safety of parenteral iron across the range of iron deficiency syndromes, clinical disease groups, and demographic populations
- Development of personalised iron supplementation strategies based on genetic loci that are associated with treatment outcomes of iron supplementation
- Clarification of clinical implications and role for screening and treatment of parenteral iron-induced hypophosphataemia
- Characterisation of possible long-term adverse effects of sustained parenteral iron therapy in patients with functional iron deficiency (including chronic kidney disease)
- Introduction of novel therapies for functional iron deficiency that inhibit hepcidin production, directly target hepcidin itself, or prevent its action on ferroportin; or promote erythropoietin production and iron transport
- Improved understanding of the benefits, risks, and optimal approaches for delivering iron to prevent and treat anaemia in children, adolescents, and women in low-income countries

women. Other strategies include deworming and delayed cord clamping to optimise infant iron stores. Infection risk complicates iron interventions in low-income settings, especially in children. Where there is high carriage of pathogenic bacteria, iron could reprofile the intestinal microbiome towards more pathogenic flora, promoting infectious diarrhoea.¹⁵⁶ In malaria-endemic settings, iron could promote malaria infection, probably because of parasite trophism for reticulocytes induced during recovery from anaemia.¹⁵⁷ WHO therefore recommends that iron supplementation should only be given in endemic settings with simultaneous malaria prevention, diagnosis, and treatment interventions.¹⁵⁸

Conclusions

Clinicians regularly encounter ID and IDA. Understanding the pathophysiology of absolute and functional ID guides diagnosis, appropriate use of established and emerging treatments, and rational deployment of further investigations. Further research into the biology, epidemiology, diagnosis, and treatment of ID (panel 2) will continue to transform approaches to this common condition.

Contributors

S-RP drafted the manuscript. All authors undertook the literature search, drafted the manuscript, and prepared the figures. S-RP was responsible for the final editing of the manuscript.

Declaration of interests

S-RP reports grants from the National Health and Medical Research Council, during the conduct of the study, and is an external advisor and a consultant to the World Health Organization, Australian Red Cross Blood Service, and Merck. DWS reports to be an employee of Radboudumc, which offers hepcidin calibration materials and high quality hepcidin measurements at a fee for service via its www.hepcidinanalysis.com initiative, and personal fees from Silence Therapeutics, outside of the submitted work. MUM reports grants and personal fees from Novartis Pharma, grants and personal fees from Silence Therapeutics, personal fees from Vifor Pharma, personal fees from Merck Selbstmedikation, and personal fees from Slovak Republic Ministry of Health, outside of the submitted work. In addition, MUM has patent 125-12ERF (Therapeutic micro RNA targets in chronic pulmonary diseases issued) and patent MJ/d 201/08 (miQPCR – a method for miRNA quantitation) issued. JT-D declares no competing interests.

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References

- Vos T, Abajobir AA, Abate KH, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017; **390**: 1211–59.
- WHO. Global nutrition targets 2025: policy brief series. 2014. https://www.who.int/nutrition/publications/globaltargets2025_policybrief_anaemia/en (accessed Nov 14, 2020).
- Ganz T. Anemia of Inflammation. *N Engl J Med* 2019; **381**: 1148–57.
- Di Angelantonio E, Thompson SG, Kaptoge S, et al. Efficiency and safety of varying the frequency of whole blood donation (INTERVAL): a randomised trial of 45 000 donors. *Lancet* 2017; **390**: 2360–71.
- Iron needs of babies and children. *Paediatr Child Health* 2007; **12**: 333–36.
- Andrews NC. Disorders of iron metabolism. *N Engl J Med* 1999; **341**: 1986–95.
- Grote Beverborg N, van der Wal HH, Klip IT, et al. Differences in clinical profile and outcomes of low iron storage vs defective iron utilization in patients with heart failure: results from the DEFINE-HF and BIOSTAT-CHF studies. *JAMA Cardiol* 2019; **4**: 696–701.
- Perera CA, Biggers RP, Robertson A. Deceitful red-flag: angina secondary to iron deficiency anaemia as a presenting complaint for underlying malignancy. *BMJ Case Rep* 2019; **12**: e229942.
- Musallam KM, Tamim HM, Richards T, et al. Preoperative anaemia and postoperative outcomes in non-cardiac surgery: a retrospective cohort study. *Lancet* 2011; **378**: 1396–407.
- Daru J, Zamora J, Fernández-Félix BM, et al. Risk of maternal mortality in women with severe anaemia during pregnancy and post partum: a multilevel analysis. *Lancet Glob Health* 2018; **6**: e548–54.
- WHO. Anaemia in children <5 years. 2017 <http://apps.who.int/gho/data/view.main.ANEMIACHILDRENRE?lang=en> (accessed Nov 14, 2020).
- WHO. Prevalence of anaemia in women. 2017 <http://apps.who.int/gho/data/node.main.ANAEMIAWOMEN?lang=en> (accessed Nov 14, 2020).
- WHO. The global prevalence of anaemia in 2011. 2015. https://www.who.int/nutrition/publications/micronutrients/global_prevalence_anaemia_2011/en/ (accessed Nov 14, 2020).
- Petry N, Olofin I, Hurrell RF, et al. The proportion of anemia associated with iron deficiency in low, medium, and high human development index countries: a systematic analysis of national surveys. *Nutrients* 2016; **8**: E693.
- Namaste SM, Rohner F, Huang J, et al. Adjusting ferritin concentrations for inflammation: biomarkers reflecting inflammation and nutritional determinants of anemia (BRINDA) project. *Am J Clin Nutr* 2017; **106** (suppl 1): 359S–71S.
- Mei Z, Cogswell ME, Looker AC, et al. Assessment of iron status in US pregnant women from the National Health and Nutrition Examination Survey (NHANES), 1999–2006. *Am J Clin Nutr* 2011; **93**: 1312–20.
- Australian Bureau of Statistics. Anemia. 4727.0.55.003—Australian Aboriginal and Torres Strait Islander health survey: biomedical results, 2012–13. 2014. <https://www.abs.gov.au/ausstats/abs@.nsf/Lookup/4727.0.55.003main+features12012-13> (accessed April 23, 2020).
- Pottie K, Greenaway C, Feightner J, et al. Evidence-based clinical guidelines for immigrants and refugees. *CMAJ* 2011; **183**: E824–925.
- Kiss JE, Birch RJ, Steele WR, Wright DJ, Cable RG. Quantification of body iron and iron absorption in the REDS-II donor iron status evaluation (RISE) study. *Transfusion* 2017; **57**: 1656–64.
- Muckenthaler MU, Rivella S, Hentze MW, Galy B. A red carpet for iron metabolism. *Cell* 2017; **168**: 344–61.
- Aschemeyer S, Qiao B, Stefanova D, et al. Structure-function analysis of ferroportin defines the binding site and an alternative mechanism of action of hepcidin. *Blood* 2018; **131**: 899–910.
- Billesbølle CB, Azumaya CM, Kretsch RC, et al. Structure of hepcidin-bound ferroportin reveals iron homeostatic mechanisms. *Nature* 2020; published online Aug 19. <https://doi.org/10.1038/s41586-020-2668-z>.
- Guida C, Altamura S, Klein FA, et al. A novel inflammatory pathway mediating rapid hepcidin-independent hypoferrremia. *Blood* 2015; **125**: 2265–75.
- Nai A, Lidonnici MR, Rausa M, et al. The second transferrin receptor regulates red blood cell production in mice. *Blood* 2015; **125**: 1170–79.
- Zhang DL, Ghosh MC, Ollivierre H, Li Y, Rouault TA. Ferroportin deficiency in erythroid cells causes serum iron deficiency and promotes hemolysis due to oxidative stress. *Blood* 2018; **132**: 2078–87.

- 26 Zhang DL, Senecal T, Ghosh MC, Ollivierre-Wilson H, Tu T, Rouault TA. Hcpidin regulates ferroportin expression and intracellular iron homeostasis of erythroblasts. *Blood* 2011; **118**: 2868–77.
- 27 Helmer OM, Emerson CP Jr. The iron content of the whole blood of normal individuals. *J Biol Chem* 1934; **104**: 157–61.
- 28 Harvey LJ, Armah CN, Dainty JR, et al. Impact of menstrual blood loss and diet on iron deficiency among women in the UK. *Br J Nutr* 2005; **94**: 557–64.
- 29 Omani Samani R, Almasi Hashiani A, Razavi M, et al. The prevalence of menstrual disorders in Iran: a systematic review and meta-analysis. *Int J Reprod Biomed* 2018; **16**: 665–78.
- 30 O'Brien B, Mason J, Kimble R. Bleeding disorders in adolescents with heavy menstrual bleeding: the Queensland Statewide Paediatric and Adolescent Gynaecology Service. *J Pediatr Adolesc Gynecol* 2019; **32**: 122–27.
- 31 Chen YC, Chao TY, Cheng SN, Hu SH, Liu JY. Prevalence of von Willebrand disease in women with iron deficiency anaemia and menorrhagia in Taiwan. *Haemophilia* 2008; **14**: 768–74.
- 32 Rockey DC, Cello JP. Evaluation of the gastrointestinal tract in patients with iron-deficiency anemia. *N Engl J Med* 1993; **329**: 1691–95.
- 33 Goddard AF, James MW, McIntyre AS, Scott BB. Guidelines for the management of iron deficiency anaemia. *Gut* 2011; **60**: 1309–16.
- 34 Kim NH, Park JH, Park DI, Sohn CI, Choi K, Jung YS. Should asymptomatic young men with iron deficiency anemia necessarily undergo endoscopy? *Korean J Intern Med* 2018; **33**: 1084–92.
- 35 Ioannou GN, Rockey DC, Bryson CL, Weiss NS. Iron deficiency and gastrointestinal malignancy: a population-based cohort study. *Am J Med* 2002; **113**: 276–80.
- 36 Eriksson C, Henriksson I, Brus O, et al. Incidence, prevalence and clinical outcome of anaemia in inflammatory bowel disease: a population-based cohort study. *Aliment Pharmacol Ther* 2018; **48**: 638–45.
- 37 Tanwar S, Lipman G, Parkes J, Macartney S. Prevalence and pathogenesis of anaemia in inflammatory bowel disease: a cross sectional study in a large tertiary centre. *Gut* 2011; **60** (suppl 1): A219–20.
- 38 Stoltzfus RJ, Chwaja HM, Tielsch JM, Schulze KJ, Albonico M, Savioli L. Epidemiology of iron deficiency anemia in Zanzibari schoolchildren: the importance of hookworms. *Am J Clin Nutr* 1997; **65**: 153–59.
- 39 Kiss JE, Vassallo RR. How do we manage iron deficiency after blood donation? *Br J Haematol* 2018; **181**: 590–603.
- 40 Salvin HE, Pasricha SR, Marks DC, Speedy J. Iron deficiency in blood donors: a national cross-sectional study. *Transfusion* 2014; **54**: 2434–44.
- 41 Dijkstra A, van den Hurk K, Bilo HJG, Slingerland RJ, Vos MJ. Repeat whole blood donors with a ferritin level of 30 µg/L or less show functional iron depletion. *Transfusion* 2019; **59**: 21–25.
- 42 Kiss JE, Brambilla D, Glynn SA, et al. Oral iron supplementation after blood donation: a randomized clinical trial. *JAMA* 2015; **313**: 575–83.
- 43 National Institutes for Health Office for Dietary Supplements. Iron. Fact sheet for professionals. 2019. <https://ods.od.nih.gov/factsheets/Iron-HealthProfessional> (accessed Nov 14, 2020).
- 44 Ahmad Fuzi SF, Koller D, Brugggraber S, Pereira DI, Dainty JR, Mushtaq S. A 1-h time interval between a meal containing iron and consumption of tea attenuates the inhibitory effects on iron absorption: a controlled trial in a cohort of healthy UK women using a stable iron isotope. *Am J Clin Nutr* 2017; **106**: 1413–21.
- 45 Haider LM, Schwingshackl L, Hoffmann G, Ekmekcioglu C. The effect of vegetarian diets on iron status in adults: a systematic review and meta-analysis. *Crit Rev Food Sci Nutr* 2018; **58**: 1359–74.
- 46 Lam JR, Schneider JL, Quesenberry CP, Corley DA. Proton pump inhibitor and histamine-2 receptor antagonist use and iron deficiency. *Gastroenterology* 2017; **152**: 821–29.e1.
- 47 Hershko C, Hoffbrand AV, Keret D, et al. Role of autoimmune gastritis, *Helicobacter pylori* and celiac disease in refractory or unexplained iron deficiency anemia. *Haematologica* 2005; **90**: 585–95.
- 48 Hooi JKY, Lai WY, Ng WK, et al. Global prevalence of *Helicobacter pylori* infection: systematic review and meta-analysis. *Gastroenterology* 2017; **153**: 420–29.
- 49 Hudak L, Jaraisy A, Haj S, Muhsen K. An updated systematic review and meta-analysis on the association between *Helicobacter pylori* infection and iron deficiency anemia. *Helicobacter* 2017; **22**: e12330.
- 50 Lebowitz B, Sanders DS, Green PHR. Celiac disease. *Lancet* 2018; **391**: 70–81.
- 51 Ludvigsson JF, Leffler DA, Bai JC, et al. The Oslo definitions for celiac disease and related terms. *Gut* 2013; **62**: 43–52.
- 52 Singh P, Arora A, Strand TA, et al. Global prevalence of celiac disease: systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2018; **16**: 823–36.e2.
- 53 Mahadev S, Laszkowska M, Sundström J, et al. Prevalence of celiac disease in patients with iron deficiency anemia—a systematic review with meta-analysis. *Gastroenterology* 2018; **155**: 374–82.e1.
- 54 Cepeda-Lopez AC, Melse-Boonstra A, Zimmermann MB, Herter-Aeberli I. In overweight and obese women, dietary iron absorption is reduced and the enhancement of iron absorption by ascorbic acid is one-half that in normal-weight women. *Am J Clin Nutr* 2015; **102**: 1389–97.
- 55 Stoffel NU, El-Mallah C, Herter-Aeberli I, et al. The effect of central obesity on inflammation, hepcidin, and iron metabolism in young women. *Int J Obes* 2020; **44**: 1291–300.
- 56 Zhao L, Zhang X, Shen Y, Fang X, Wang Y, Wang F. Obesity and iron deficiency: a quantitative meta-analysis. *Obes Rev* 2015; **16**: 1081–93.
- 57 Finberg KE, Heeney MM, Campagna DR, et al. Mutations in TMPRSS6 cause iron-refractory iron deficiency anemia (IRIDA). *Nat Genet* 2008; **40**: 569–71.
- 58 Gichohi-Wainaina WN, Towers GW, Swinkels DW, Zimmermann MB, Feskens EJ, Melse-Boonstra A. Inter-ethnic differences in genetic variants within the transmembrane protease, serine 6 (TMPRSS6) gene associated with iron status indicators: a systematic review with meta-analyses. *Genes Nutr* 2015; **10**: 442.
- 59 Cercamondi CI, Egli IM, Ahouandjinou E, et al. Afebrile *Plasmodium falciparum* parasitemia decreases absorption of fortification iron but does not affect systemic iron utilization: a double stable-isotope study in young Beninese women. *Am J Clin Nutr* 2010; **92**: 1385–92.
- 60 Prentice AM, Bah A, Jallow MW, et al. Respiratory infections drive hepcidin-mediated blockade of iron absorption leading to iron deficiency anemia in African children. *Sci Adv* 2019; **5**: eaav9020.
- 61 Aksan A, Wohlrath M, Iqbal TH, Dignass A, Stein J. Inflammation, but not the underlying disease or its location, predicts oral iron absorption capacity in patients with inflammatory bowel disease. *J Crohns Colitis* 2020; **14**: 316–22.
- 62 Lönnerdal B. Development of iron homeostasis in infants and young children. *Am J Clin Nutr* 2017; **106** (suppl 6): 1575–80S.
- 63 Moreno-Fernandez J, Ochoa JJ, Latunde-Dada GO, Diaz-Castro J. Iron deficiency and iron homeostasis in low birth weight preterm infants: a systematic review. *Nutrients* 2019; **11**: E1090.
- 64 McDonald SJ, Middleton P, Dowswell T, Morris PS. Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. *Cochrane Database Syst Rev* 2013; **7**: CD004074.
- 65 Armitage AE, Agbla SC, Betts M, et al. Rapid growth is a dominant predictor of hepcidin suppression and declining ferritin in Gambian infants. *Haematologica* 2019; **104**: 1542–53.
- 66 Obbagy JE, English LK, Psota TL, et al. Complementary feeding and micronutrient status: a systematic review. *Am J Clin Nutr* 2019; **109** (suppl 7): 852–71S.
- 67 Bothwell TH. Iron requirements in pregnancy and strategies to meet them. *Am J Clin Nutr* 2000; **72** (suppl): 257–64S.
- 68 Centers for Disease Control and Prevention. Recommendations to prevent and control iron deficiency in the United States. *MMWR Recomm Rep* 1998; **47**: 1–29.
- 69 Barrett JF, Whittaker PG, Williams JG, Lind T. Absorption of non-haem iron from food during normal pregnancy. *BMJ* 1994; **309**: 79–82.
- 70 Bah A, Pasricha SR, Jallow MW, et al. serum hepcidin concentrations decline during pregnancy and may identify iron deficiency: analysis of a longitudinal pregnancy cohort in The Gambia. *J Nutr* 2017; **147**: 1131–37.
- 71 Young MF, Griffin I, Pressman E, et al. Maternal hepcidin is associated with placental transfer of iron derived from dietary heme and nonheme sources. *J Nutr* 2012; **142**: 33–39.

- 72 Sim M, Garvican-Lewis LA, Cox GR, et al. Iron considerations for the athlete: a narrative review. *Eur J Appl Physiol* 2019; **119**: 1463–78.
- 73 Moretti D, Mettler S, Zeder C, et al. An intensified training schedule in recreational male runners is associated with increases in erythropoiesis and inflammation and a net reduction in plasma hepcidin. *Am J Clin Nutr* 2018; **108**: 1324–33.
- 74 Peyrin-Biroulet L, Williet N, Cacoub P. Guidelines on the diagnosis and treatment of iron deficiency across indications: a systematic review. *Am J Clin Nutr* 2015; **102**: 1585–94.
- 75 Hallberg L, Bengtsson C, Lapidus L, Lindstedt G, Lundberg PA, Hultén L. Screening for iron deficiency: an analysis based on bone-marrow examinations and serum ferritin determinations in a population sample of women. *Br J Haematol* 1993; **85**: 787–98.
- 76 WHO. WHO guideline on use of ferritin concentrations to assess iron status in individuals and populations. 2020. <https://www.who.int/publications/i/item/9789240000124> (accessed Nov 14, 2020).
- 77 Darton TC, Blohmke CJ, Giannoulatou E, et al. Rapidly escalating hepcidin and associated serum iron starvation are features of the acute response to typhoid infection in humans. *PLoS Negl Trop Dis* 2015; **9**: e0004029.
- 78 Williams AM, Ladva CN, Leon JS, et al. Changes in micronutrient and inflammation serum biomarker concentrations after a norovirus human challenge. *Am J Clin Nutr* 2019; **110**: 1456–64.
- 79 Namaste S, Richardson B, Ssebiro F, Kantuntu D, Vosti S, D'Agostino A. Comparing the effectiveness and cost-effectiveness of facility- versus community-based distribution of micronutrient powders in rural Uganda. IUNS 21st International Congress of Nutrition. Buenos Aires, Argentina; Oct 15–20, 2017.
- 80 McKinnon EJ, Rossi E, Beilby JP, Trinder D, Olynyk JK. Factors that affect serum levels of ferritin in Australian adults and implications for follow-up. *Clin Gastroenterol Hepatol* 2014; **12**: 101–08.e4.
- 81 Infusino I, Braga F, Dolci A, Panteghini M. Soluble transferrin receptor (sTfR) and sTfR/log ferritin index for the diagnosis of iron-deficiency anemia. A meta-analysis. *Am J Clin Pathol* 2012; **138**: 642–49.
- 82 Urrechaga E, Boveda O, Aguayo FJ, et al. Percentage of hypochromic erythrocytes and reticulocyte hemoglobin equivalent predictors of response to intravenous iron in hemodialysis patients. *Int J Lab Hematol* 2016; **38**: 360–65.
- 83 Ullrich C, Wu A, Armsby C, et al. Screening healthy infants for iron deficiency using reticulocyte hemoglobin content. *JAMA* 2005; **294**: 924–30.
- 84 Thomas DW, Hinchliffe RF, Briggs C, Macdougall IC, Littlewood T, Cavill I. Guideline for the laboratory diagnosis of functional iron deficiency. *Br J Haematol* 2013; **161**: 639–48.
- 85 Girelli D, Nemeth E, Swinkels DW. Hepcidin in the diagnosis of iron disorders. *Blood* 2016; **127**: 2809–13.
- 86 Pasricha SR, Atkinson SH, Armitage AE, et al. Expression of the iron hormone hepcidin distinguishes different types of anemia in African children. *Sci Transl Med* 2014; **6**: 235re3.
- 87 Lasocki S, Baron G, Driss F, et al. Diagnostic accuracy of serum hepcidin for iron deficiency in critically ill patients with anemia. *Intensive Care Med* 2010; **36**: 1044–48.
- 88 Shu T, Jing C, Lv Z, Xie Y, Xu J, Wu J. Hepcidin in tumor-related iron deficiency anemia and tumor-related anemia of chronic disease: pathogenic mechanisms and diagnosis. *Eur J Haematol* 2015; **94**: 67–73.
- 89 Bregman DB, Morris D, Koch TA, He A, Goodnough LT. Hepcidin levels predict non responsiveness to oral iron therapy in patients with iron deficiency anemia. *Am J Hematol* 2013; **88**: 97–101.
- 90 Diepeveen LE, Laarakkers CMM, Martos G, et al. Provisional standardization of hepcidin assays: creating a traceability chain with a primary reference material, candidate reference method and a commutable secondary reference material. *Clin Chem Lab Med* 2019; **57**: 864–72.
- 91 Al-Toma A, Volta U, Auricchio R, et al. European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders. *United European Gastroenterol J* 2019; **7**: 583–613.
- 92 Ko CW, Siddique SM, Patel A, et al. AGA Clinical practice guidelines on the gastrointestinal evaluation of iron deficiency anemia. *Gastroenterology* 2020; **159**: 1085–94.
- 93 Tolkien Z, Stecher L, Mander AP, Pereira DI, Powell JJ. Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: a systematic review and meta-analysis. *PLoS One* 2015; **10**: e0117383.
- 94 Pasricha SR, Marks DC, Salvin H, et al. Postdonation iron replacement for maintaining iron stores in female whole blood donors in routine donor practice: results of two feasibility studies in Australia. *Transfusion* 2017; **57**: 1922–29.
- 95 Pasricha SR, Flecknoe-Brown SC, Allen KJ, et al. Diagnosis and management of iron deficiency anaemia: a clinical update. *Med J Aust* 2010; **193**: 525–32.
- 96 Moretti D, Goede JS, Zeder C, et al. Oral iron supplements increase hepcidin and decrease iron absorption from daily or twice-daily doses in iron-depleted young women. *Blood* 2015; **126**: 1981–89.
- 97 Stoffel NU, Cercamondi CI, Brittenham G, et al. Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomised controlled trials. *Lancet Haematol* 2017; **4**: e524–33.
- 98 Stoffel NU, Zeder C, Brittenham GM, Moretti D, Zimmermann MB. Iron absorption from supplements is greater with alternate day than with consecutive day dosing in iron-deficient anemic women. *Haematologica* 2020; **105**: 1232–39.
- 99 Kaundal R, Bhatia P, Jain A, et al. Randomized controlled trial of twice-daily versus alternate-day oral iron therapy in the treatment of iron-deficiency anemia. *Ann Hematol* 2020. **99**: 57–63.
- 100 Pergola PE, Fishbane S, Ganz T. Novel oral iron therapies for iron deficiency anemia in chronic kidney disease. *Adv Chronic Kidney Dis* 2019; **26**: 272–91.
- 101 Gómez-Ramírez S, Brilli E, Tarantino G, Muñoz M. Sucrosomial® iron: a new generation iron for improving oral supplementation. *Pharmaceuticals (Basel)* 2018; **11**: E97.
- 102 Pereira DIA, Mohammed NI, Ofordile O, et al. A novel nano-iron supplement to safely combat iron deficiency and anaemia in young children: the IHAT-GUT double-blind, randomised, placebo-controlled trial protocol. *Gates Open Res* 2018; **2**: 48.
- 103 Girelli D, Ugolini S, Busti F, Marchi G, Castagna A. Modern iron replacement therapy: clinical and pathophysiological insights. *Int J Hematol* 2018; **107**: 16–30.
- 104 Avni T, Bieber A, Grossman A, Green H, Leibovici L, Gafter-Gvili A. The safety of intravenous iron preparations: systematic review and meta-analysis. *Mayo Clin Proc* 2015; **90**: 12–23.
- 105 US Food and Drug Administration. INJECTAFER (ferric carboxymaltose injection), for intravenous use. Initial US approval. 2013. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/203565s0091bl.pdf (accessed Nov 14, 2020).
- 106 Canning ML, Gilmore KA. Iron stain following an intravenous iron infusion. *Med J Aust* 2017; **207**: 58.
- 107 Calvet X, Ruiz MA, Dosal A, et al. Cost-minimization analysis favours intravenous ferric carboxymaltose over ferric sucrose for the ambulatory treatment of severe iron deficiency. *PLoS One* 2012; **7**: e45604.
- 108 Friedrisch JR, Cançado RD. Intravenous ferric carboxymaltose for the treatment of iron deficiency anemia. *Rev Bras Hematol Hemoter* 2015; **37**: 400–05.
- 109 Adkinson NF, Strauss WE, Macdougall IC, et al. Comparative safety of intravenous ferumoxytol versus ferric carboxymaltose in iron deficiency anemia: a randomized trial. *Am J Hematol* 2018; **93**: 683–90.
- 110 Wolf M, Chertow GM, Macdougall IC, Kaper R, Krop J, Strauss W. Randomized trial of intravenous iron-induced hypophosphatemia. *JCI Insight* 2018; **3**: 124486.
- 111 Fang W, Kenny R, Rizvi QU, McMahon LP, Garg M. Hypophosphataemia after ferric carboxymaltose is unrelated to symptoms, intestinal inflammation or vitamin D status. *BMC Gastroenterol* 2020; **20**: 183.
- 112 Vandemergel X, Vanderghenst F. Potentially life-threatening phosphate diabetes induced by ferric carboxymaltose injection: a case report and review of the literature. *Case Rep Endocrinol* 2014; **2014**: 843689.
- 113 Klein K, Asaad S, Econs M, Rubin JE. Severe FGF23-based hypophosphataemic osteomalacia due to ferric carboxymaltose administration. *BMJ Case Rep* 2018; **2018**: bcr2017222851.

- 114 Dailymed. FERAHEME—ferumoxytol injection. 2020. <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=32b0e320-a739-11dc-a704-0002a5d5c51b> (accessed Nov 14, 2020).
- 115 Karki NR, Auerbach M. Single total dose infusion of ferumoxytol (1020 mg in 30 minutes) is an improved method of administration of intravenous iron. *Am J Hematol* 2019; **94**: E229–31.
- 116 Wolf M, Rubin J, Achebe M, et al. Effects of iron isomaltoside vs ferric carboxymaltose on hypophosphatemia in iron-deficiency anemia: two randomized clinical trials. *JAMA* 2020; **323**: 432–43.
- 117 Auerbach M, Pappadakis JA, Bahrain H, Auerbach SA, Ballard H, Dahl NV. Safety and efficacy of rapidly administered (one hour) one gram of low molecular weight iron dextran (INFeD) for the treatment of iron deficient anemia. *Am J Hematol* 2011; **86**: 860–62.
- 118 Garg M, Morrison G, Friedman A, Lau A, Lau D, Gibson PR. A rapid infusion protocol is safe for total dose iron polymaltose: time for change. *Intern Med J* 2011; **41**: 548–54.
- 119 Pavord S, Daru J, Prasannan N, et al. UK guidelines on the management of iron deficiency in pregnancy. *Br J Haematol* 2020; **188**: 819–30.
- 120 Powers JM, Shamoun M, McCavit TL, Adix L, Buchanan GR. intravenous ferric carboxymaltose in children with iron deficiency anemia who respond poorly to oral iron. *J Pediatr* 2017; **180**: 212–16.
- 121 Clevenger B, Gurusamy K, Klein AA, Murphy GJ, Anker SD, Richards T. Systematic review and meta-analysis of iron therapy in anaemic adults without chronic kidney disease: updated and abridged Cochrane review. *Eur J Heart Fail* 2016; **18**: 774–85.
- 122 Low MS, Speedy J, Styles CE, De-Regil LM, Pasricha SR. Daily iron supplementation for improving anaemia, iron status and health in menstruating women. *Cochrane Database Syst Rev* 2016; **4**: CD009747.
- 123 Peña-Rosas JP, De-Regil LM, Garcia-Casal MN, Dowswell T. Daily oral iron supplementation during pregnancy. *Cochrane Database Syst Rev* 2015; **7**: CD004736.
- 124 Pasricha SR, Hayes E, Kalumba K, Biggs BA. Effect of daily iron supplementation on health in children aged 4–23 months: a systematic review and meta-analysis of randomised controlled trials. *Lancet Glob Health* 2013; **1**: e77–86.
- 125 Low M, Farrell A, Biggs BA, Pasricha SR. Effects of daily iron supplementation in primary-school-aged children: systematic review and meta-analysis of randomized controlled trials. *CMAJ* 2013; **185**: E791–802.
- 126 Houston BL, Hurrie D, Graham J, et al. Efficacy of iron supplementation on fatigue and physical capacity in non-anaemic iron-deficient adults: a systematic review of randomised controlled trials. *BMJ Open* 2018; **8**: e019240.
- 127 Pasricha SR, Low M, Thompson J, Farrell A, De-Regil LM. Iron supplementation benefits physical performance in women of reproductive age: a systematic review and meta-analysis. *J Nutr* 2014; **144**: 906–14.
- 128 Burden RJ, Pollock N, Whyte GP, et al. Effect of intravenous iron on aerobic capacity and iron metabolism in elite athletes. *Med Sci Sports Exerc* 2015; **47**: 1399–407.
- 129 Avni T, Reich S, Lev N, Gaftor-Gvili A. Iron supplementation for restless legs syndrome—a systematic review and meta-analysis. *Eur J Intern Med* 2019; **63**: 34–41.
- 130 Mwangi MN, Roth JM, Smit MR, et al. Effect of daily antenatal iron supplementation on plasmodium infection in Kenyan women: a randomized clinical trial. *JAMA* 2015; **314**: 1009–20.
- 131 Lewkowitz AK, Gupta A, Simon L, et al. Intravenous compared with oral iron for the treatment of iron-deficiency anemia in pregnancy: a systematic review and meta-analysis. *J Perinatol* 2019; **39**: 519–32.
- 132 Qassim A, Grivell RM, Henry A, Kidson-Gerber G, Shand A, Grzeskowiak LE. Intravenous or oral iron for treating iron deficiency anaemia during pregnancy: systematic review and meta-analysis. *Med J Aust* 2019; **211**: 367–73.
- 133 WHO. WHO recommendations on antenatal care for a positive pregnancy experience. 2016. <https://www.who.int/publications/i/item/9789241549912> (accessed Nov 14, 2020).
- 134 Achebe MM, Gaftor-Gvili A. How I treat anemia in pregnancy: iron, cobalamin, and folate. *Blood* 2017; **129**: 940–49.
- 135 Sultan P, Bampoe S, Shah R, et al. Oral vs intravenous iron therapy for postpartum anemia: a systematic review and meta-analysis. *Am J Obstet Gynecol* 2019; **221**: 19–29.e3.
- 136 Anker SD, Comin Colet J, Filippatos G, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med* 2009; **361**: 2436–48.
- 137 Ponikowski P, van Veldhuisen DJ, Comin-Colet J, et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. *Eur Heart J* 2015; **36**: 657–68.
- 138 Zhou X, Xu W, Xu Y, Qian Z. Iron supplementation improves cardiovascular outcomes in patients with heart failure. *Am J Med* 2019; **132**: 955–63.
- 139 Lewis GD, Malhotra R, Hernandez AF, et al. Effect of oral iron repletion on exercise capacity in patients with heart failure with reduced ejection fraction and iron deficiency: the IRONOUT HF randomized clinical trial. *JAMA* 2017; **317**: 1958–66.
- 140 Ponikowski P, Kirwan B-A, Anker SD, et al. Ferric carboxymaltose for iron deficiency at discharge after acute heart failure: a multicentre, double-blind, randomised, controlled trial. *Lancet* 2020; published online Nov 13. [https://doi.org/10.1016/S0140-6736\(20\)32339-4](https://doi.org/10.1016/S0140-6736(20)32339-4).
- 141 Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; **37**: 2129–200.
- 142 Bonovas S, Fiorino G, Allocca M, et al. Intravenous versus oral iron for the treatment of anemia in inflammatory bowel disease: a systematic review and meta-analysis of randomized controlled trials. *Medicine (Baltimore)* 2016; **95**: e2308.
- 143 Mueller MM, Van Remoortel H, Meybohm P, et al. Patient blood management: recommendations from the 2018 Frankfurt Consensus Conference. *JAMA* 2019; **321**: 983–97.
- 144 Ng O, Keeler BD, Mishra A, et al. Iron therapy for pre-operative anaemia. *Cochrane Database Syst Rev* 2015; **12**: CD011588.
- 145 Richards T, Baikady RR, Clevenger B, et al. Preoperative intravenous iron to treat anaemia before major abdominal surgery (PREVENTT): a randomised, double-blind, controlled trial. *Lancet* 2020; published online Sept 4. [https://doi.org/10.1016/S0140-6736\(20\)31539-7](https://doi.org/10.1016/S0140-6736(20)31539-7).
- 146 Muñoz M, Acheson AG, Auerbach M, et al. International consensus statement on the peri-operative management of anaemia and iron deficiency. *Anaesthesia* 2017; **72**: 233–47.
- 147 Khalafallah AA, Yan C, Al-Badri R, et al. Intravenous ferric carboxymaltose versus standard care in the management of postoperative anaemia: a prospective, open-label, randomised controlled trial. *Lancet Haematol* 2016; **3**: e415–25.
- 148 Bisbe E, Moltó L, Arroyo R, Muniesa JM, Tejero M. Randomized trial comparing ferric carboxymaltose vs oral ferrous glycine sulphate for postoperative anaemia after total knee arthroplasty. *Br J Anaesth* 2014; **113**: 402–09.
- 149 Perelman I, Winter R, Sikora L, Martel G, Saidenberg E, Fergusson D. The efficacy of postoperative iron therapy in improving clinical and patient-centered outcomes following surgery: a systematic review and meta-analysis. *Transfus Med Rev* 2018; **32**: 89–101.
- 150 O'Lone EL, Hodson EM, Nistor I, Bolognani D, Webster AC, Craig JC. Parenteral versus oral iron therapy for adults and children with chronic kidney disease. *Cochrane Database Syst Rev* 2019; **2**: CD007857.
- 151 Macdougall IC, White C, Anker SD, et al. intravenous iron in patients undergoing maintenance hemodialysis. *N Engl J Med* 2019; **380**: 447–58.
- 152 Block GA, Fishbane S, Rodriguez M, et al. A 12-week, double-blind, placebo-controlled trial of ferric citrate for the treatment of iron deficiency anemia and reduction of serum phosphate in patients with CKD Stages 3–5. *Am J Kidney Dis* 2015; **65**: 728–36.
- 153 Fishbane S, Block GA, Loran L, et al. Effects of ferric citrate in patients with nondialysis-dependent CKD and iron deficiency anemia. *J Am Soc Nephrol* 2017; **28**: 1851–58.
- 154 Pasricha SR, Drakesmith H, Black J, Hipgrave D, Biggs BA. Control of iron deficiency anemia in low- and middle-income countries. *Blood* 2013; **121**: 2607–17.

- 155 WHO. Nutritional anaemias: tools for effective prevention and control. 2017. <https://www.who.int/publications/i/item/9789241513067> (accessed Nov 14, 2020).
- 156 Jaeggi T, Kortman GA, Moretti D, et al. Iron fortification adversely affects the gut microbiome, increases pathogen abundance and induces intestinal inflammation in Kenyan infants. *Gut* 2015; **64**: 731–42.
- 157 Clark MA, Goheen MM, Fulford A, et al. Host iron status and iron supplementation mediate susceptibility to erythrocytic stage *Plasmodium falciparum*. *Nat Commun* 2014; **5**: 4446.
- 158 WHO. Daily iron supplementation in children 6–23 months of age in malaria-endemic areas. 2019. <https://www.who.int/elena/titles/iron-children-6to23-malaria/en/> (accessed Nov 14, 2020).

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