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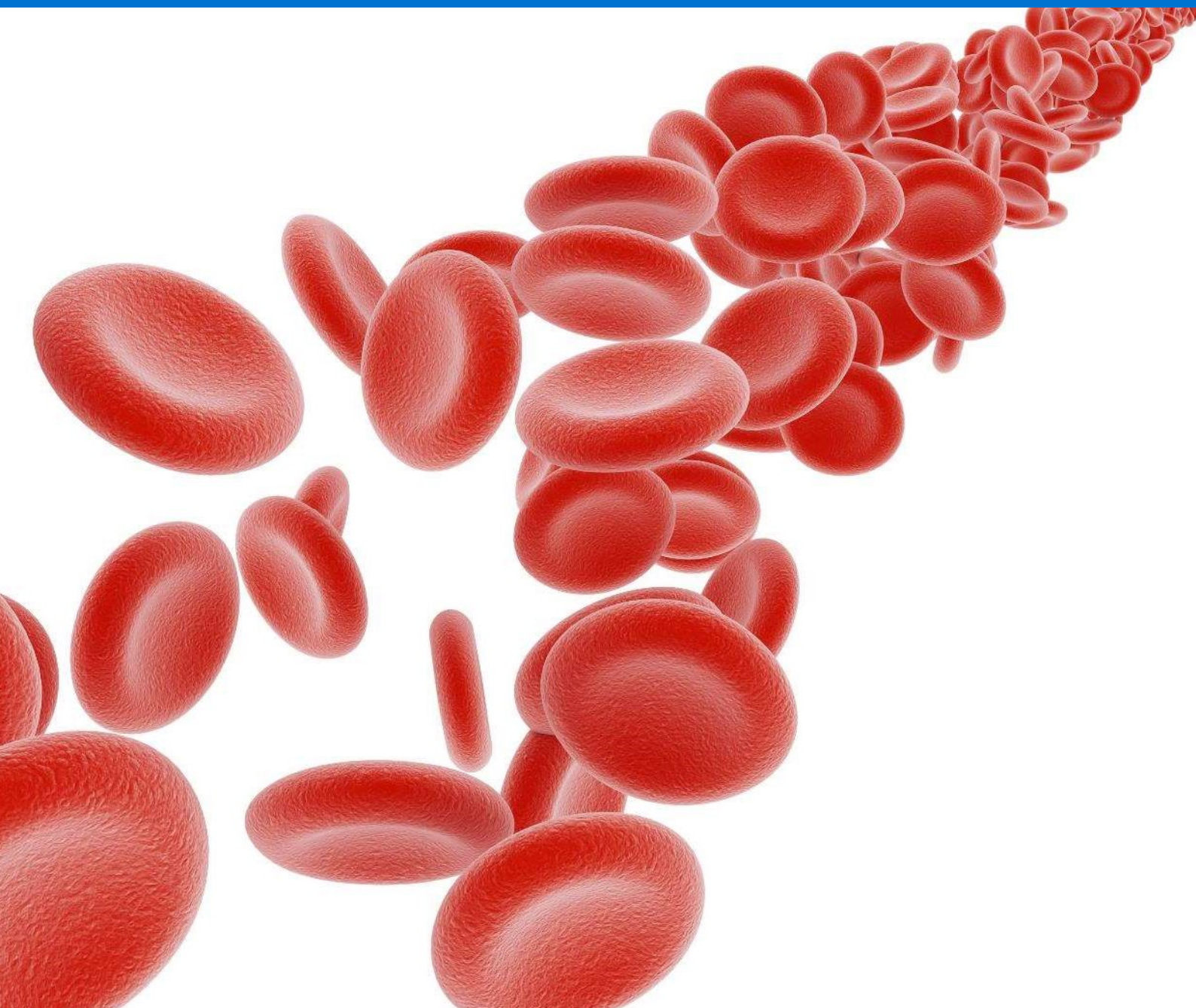
Clinical Update for
General Practitioners and Physicians

Iron Deficiency

Updated 2022



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This document has been prepared by the Gastroenterological Society of Australia, and every care has been taken in its development. The document is intended only for use by clinicians as a guide in relation to iron deficiency and not as an authoritative statement on every conceivable step or circumstance which may or could relate to the management of iron deficiency. Medical understanding of iron deficiency is evolving. This document reflects this understanding as of November 2022 and may be subject to updating and review at a later date.

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This clinical update is intended for general practitioners and general physicians and thus does not deal with the finer points of endoscopic investigation of iron deficiency with or without anaemia. However, it should be emphasised that, in general, all people with confirmed iron deficiency should be screened for coeliac disease and all adults referred for gastrointestinal assessment and considered for upper and lower gastrointestinal endoscopy UNLESS there is a history of obvious, recent significant non-gastrointestinal blood loss. This requires good clinical judgement; however, serious gastrointestinal disease as the cause of iron deficiency should always be considered.

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Contents

1. Overview

Iron deficiency is the most common nutritional deficiency worldwide and accounts for about half of the global burden of anaemia.[1] It may also result in fatigue, reduced cognitive function, hair loss, glossitis, stomatitis or restless legs in the absence of anaemia.

Iron deficiency may occur at all ages, but particularly susceptible groups include children, women after the onset of menstruation, elderly people, vegetarians (especially vegans) and disadvantaged populations, such as Indigenous Australians, refugees, recent migrants and people in institutions.[2-5]

Iron deficiency anaemia can be absolute or functional. Absolute iron deficiency with anaemia occurs when iron stores in the bone marrow and monocyte–macrophage system are insufficient for erythropoiesis. Functional iron deficiency with anaemia occurs when iron stores are normal or increased but there is insufficient supply of iron for erythropoiesis.

Management of iron deficiency entails both investigation of its cause and replacement of iron.

Iron deficiency may indicate a serious disease, and anaemia might not be present with early iron deficiency. Absolute iron deficiency results from:

- inadequate dietary oral intake
- malabsorption of iron
- excess iron loss (bleeding), which may be overt or occult.

More than one cause may be present in some patients.

Patients should generally be referred to a gastroenterologist for evaluation of the cause of iron deficiency with or without anaemia, as gastrointestinal bleeding is the most common cause of iron deficiency in all age groups except premenopausal women.

Replacement of iron comprises oral or intravenous iron therapy. Increase in dietary iron intake alone may be insufficient to correct iron deficiency, but it has an important role in primary and secondary prevention of iron deficiency.

2. Definitions

Iron: Divalent cation, metallic element; an essential micronutrient involved in oxygen transport within the body and the regulation of cell growth and differentiation.

Iron deficiency: The state of inadequate body iron stores. A serum ferritin level < 30 µg/L is the single best marker of reduced body iron status.[6]

Anaemia: A blood haemoglobin level below normal, defined by the World Health Organization as < 130 g/L in adult men, < 120 g/L in adult women and < 110 g/L in pregnant women.[4] Anaemia may be caused by multiple conditions other than iron deficiency.

Iron deficiency anaemia: An advanced stage of iron depletion, resulting in inadequate erythropoiesis.

- ***Absolute iron deficiency with anaemia*** occurs when iron stores in the bone marrow and monocyte–macrophage system are insufficient for erythropoiesis. The serum ferritin level is < 30 µg/L.
- ***Functional iron deficiency with anaemia*** occurs when iron stores are normal or increased but there is insufficient supply of iron for erythropoiesis. This occurs in states of systemic inflammation and chronic kidney disease. The serum ferritin level is 30–100 µg/L (and may be higher), with an elevated C-reactive protein level and/or transferrin saturation < 20%.

Iron status: The current state of iron balance in an individual. There is a continuum from iron deficiency with anaemia to iron deficiency without anaemia, to normal iron status and finally to iron overload, which can cause organ damage when severe.

- ***Iron replete:*** A serum ferritin level ≥ 30 µg/L in the absence of inflammation.

The terms iron deficiency, iron deficiency anaemia, and anaemia should not be used interchangeably.

3. Basic Iron Physiology

Iron intake and absorption

Dietary iron is absorbed in the duodenum and proximal jejunum. Iron absorption can be upregulated in states of iron deficiency and downregulated in states of excess. Multiple mediators, including the peptide hepcidin, are involved in this process.[4]

Food provides iron in two forms: haem and non-haem. Haem iron is better absorbed than non-haem iron (about 15–35% vs < 10%).[4,7]

Haem iron is derived from red meats (beef, lamb, veal, pork), organ meats (liver, kidney) and, to a lesser extent, poultry and fish. Non-haem iron is found in eggs, nuts, grains (rice, maize, wheat), fortified cereals, pulses (black beans, lentils), green leafy vegetables (spinach, silver beet, broccoli) and soybeans.

The difference in absorption rates of haem and non-haem iron accounts for the higher frequency of iron deficiency in vegetarians and vegans.

Absorption of non-haem iron may be increased by co-consumption of foods rich in vitamin C and other organic acids (citrus fruits and juices, strawberries, kiwifruit, pawpaw, melons, green leafy vegetables, tomatoes and capsicum).

Absorption of non-haem iron may be reduced by tannins (found in tea and coffee), polyphenols (found in red wine), soy proteins, and phytates and fibres in wholegrains. It is therefore recommended that susceptible individuals separate tea and coffee from meals. Calcium-rich foods and calcium supplements can inhibit the absorption of both haem and non-haem iron in foods.

***Recommended dietary intake of iron*[8]**

- Infants aged 0–6 months: 0.2 mg/day
- Children and most adults: 8–11 mg/day
- Women and girls of reproductive age: 15–18 mg/day
- Pregnant women: 27 mg/day

Iron storage

Iron is an important component of haemoglobin, myoglobin and many other enzymes essential to aerobic cellular metabolism. Almost two-thirds of the body's iron is found in haemoglobin present in circulating erythrocytes, and another quarter in readily metabolised stores as ferritin or haemosiderin in the liver and reticuloendothelial system. The remaining iron is in the myoglobin of muscle tissue and various enzymes necessary for oxidative metabolism and other cell functions.[9]

Iron excretion

During normal iron homeostasis, most iron is lost via shedding of duodenal enterocytes, with a small amount lost in urine, sweat and skin cells.

4. Causes of Iron Deficiency

There are three main mechanisms for the development of iron deficiency. More than one cause may be present in a person.

Excessive blood loss

Blood loss is also iron loss. At a population level in Australia, the most common cause of excess blood loss is heavy menstrual periods (menorrhagia) in women.

In men and postmenopausal women, the most likely causes of chronic blood loss are upper gastrointestinal erosions or ulcers related to aspirin or other non-steroidal anti-inflammatory drug (NSAID) use, gastrointestinal angioectasia or dysplasia, colonic polyps and bowel cancer.

Other situations causing blood loss may be regular blood donation, unexpectedly large perioperative blood loss, gastrointestinal conditions such as inflammatory bowel disease (Crohn's disease or ulcerative colitis) or chronic enteric infection with parasites such as hookworms. Urinary tract blood loss should also be considered.

Inadequate iron intake in the diet

Iron intake is highly variable across Australian diets. Consumption of red meat (60–100 g) at least three times a week meets most dietary requirements. Vegetarians need to consume about 80% more iron to meet requirements, given the lower absorption of non-haem iron.[8]

Inadequate iron absorption by the gut

Malabsorption of iron can be caused by:

- coeliac disease (damaged/reduced small intestinal absorptive surface)
- other inflammatory intestinal disorders, such as Crohn's disease, Whipple disease, tropical sprue or autoimmune enteropathy (upregulation of hepcidin with inflammation may also contribute to functional iron deficiency)
- gastric surgery, including bariatric surgery (banding or bypass)
- achlorhydria from extensive gastric atrophy (usually only seen if dietary iron intake is also marginal) or, uncommonly, gastric acid suppression.

5. Risk Groups

General population

- Pregnant women (rapid fetal growth creates a higher iron requirement)
- Adolescent girls and women of childbearing age (especially those with heavy menstrual blood loss)
- Young children (rapid growth creates a higher iron requirement)
- People on a vegetarian or vegan diet
- Regular blood donors
- Socially disadvantaged people (due to cost and limited knowledge of food preparation), including elderly people, Indigenous Australians, refugees and migrants from economically disadvantaged nations
- Athletes (elite level)

People with gastrointestinal disease resulting in malabsorption or blood loss

- Dysphagia, oesophagitis
- Gastric ulceration, cancer, previous gastric or bariatric surgery, achlorhydria
- Aspirin/NSAID enteropathy, angioectasia
- Coeliac disease, inflammatory bowel disease, chronic gastrointestinal infections (e.g. *Giardia*, hookworm)
- Bowel cancer

Other at-risk groups

- Children with chronic disease
- People with chronic kidney disease (especially those on haemodialysis) or urinary tract blood loss
- People with poor dentition

Adult men and postmenopausal women lose very little iron and have a low risk of iron deficiency. Therefore, iron deficiency in these groups should always be investigated for sources of blood loss from the gastrointestinal tract. Both upper and lower gastrointestinal endoscopies are usually necessary. Iron deficiency can be the ONLY manifestation of gastrointestinal diagnoses, including cancer.

6. Clinical Consequences and Symptoms

Iron deficiency may be asymptomatic or may result in:

- **Haematological manifestations** (anaemia)
- **Non-haematological manifestations** (presumed to be caused by deficiency of iron-containing cellular enzymes, especially in muscle and brain):
  - decreased memory and impaired learning, concentration and cognition
  - fatigue
  - adverse pregnancy outcomes (for mother and baby)
  - infant developmental delay
  - impaired immune function
  - glossitis
  - pica or picophagia
  - childhood obesity.

7. Prognosis

There is no single definitive marker of iron deficiency, and testing for iron stores in high-risk patients or those with symptoms suggesting iron deficiency is recommended.

Iron studies, full blood examination and assessment for systemic inflammation (measurement of C-reactive protein level) should be requested if iron deficiency is suspected.

Iron therapy should not be instituted without confirming the presence of iron deficiency.

The following represents a typical profile of iron studies in a patient with iron deficiency:

- low serum ferritin level
- low serum iron level
- raised total transferrin level or total iron-binding capacity
- decreased transferrin saturation.

Serum ferritin is the most sensitive and specific marker of iron deficiency. A ferritin concentration < 30 µg/L for adults and < 15 µg/L for children is diagnostic of iron deficiency. In adults without concurrent inflammation, a serum ferritin level < 12 µg/L has been shown to have sensitivity of 25% and specificity of 98%, and a serum ferritin level < 30 µg/L had sensitivity of 92% and specificity of 98%.[6]

Ferritin is also an acute phase reactant. Therefore, its level may be raised several-fold, approaching 100–150 µg/L, in the presence of inflammation and malignancy, even in states of iron deficiency. Ferritin levels may also increase in people with hepatic or splenic cell damage. Adding further complexity, functional iron deficiency may occur at these or higher serum ferritin levels, where availability of iron for erythropoiesis is limited (overlapping with anaemia of chronic disease).

To assess for iron deficiency in the presence of inflammation, additional markers, such as transferrin saturation (which may be low, below 20%) and C-reactive protein, may be useful. Measurements of other indices, such as soluble transferrin receptor, soluble transferrin receptor to log ferritin ratio and circulating hepcidin levels, have been published but are rarely used in clinical practice.[10,11] A bone marrow biopsy may rarely be required.

Additionally, assessment for anaemia (haemoglobin < 130 g/L in adult men, < 120 g/L in adult women and < 110 g/L in pregnant women), microcytosis (reduced mean corpuscular volume) and hypochromia (reduced mean corpuscular haemoglobin) should be done, especially looking for trends over time.

It is important to note that anaemia occurs late in the stages of iron deficiency.

Iron deficiency is not a diagnosis in itself but requires further investigation for a cause.

8. Management of Iron Deficiency

Management of iron deficiency comprises both:

- diagnosis and treatment of the underlying disorder that led to the iron deficiency
- replacement of iron.

Diagnosis of the cause

Diagnosis of the cause of iron deficiency requires taking a careful history and usually involves referral to a specialist gastroenterologist for consideration of upper and lower endoscopies and, if these are normal, capsule endoscopy. Coeliac serology should be performed for most individuals.

The degree of anaemia should determine the urgency and extent of investigation, as severe anaemia does not often result from simple causes (e.g. menstrual blood loss, vegetarian diet) in isolation.

Iron replacement

Iron replacement may be achieved by:

- dietary modification
- oral iron supplementation
- parenteral (intravenous) iron therapy.

The urgency with which iron replacement is undertaken depends on:

- the degree of iron deficiency and/or anaemia
- the presence of intercurrent cardiorespiratory disease (making restoration of adequate oxygen-carrying capacity more urgent).

Blood transfusions should only be considered in cases of severe symptomatic iron deficiency anaemia with clinical sequelae of reduced oxygen-carrying capacity or ongoing bleeding.

The aim of treatment should be to restore haemoglobin levels and red cell indices to normal and to replenish body iron stores.

Dietary modification

Dietary modification is of limited efficacy in correcting established iron deficiency, but it should be advised for primary or secondary prevention.[12]

Oral iron supplementation

Oral iron tablets or liquids are composed of salts of iron, with ferrous sulfate, iron polymaltose (ferric hydroxide with polymaltose), ferrous gluconate and ferrous fumarate the most commonly available formulations.

Oral iron has been shown to improve haemoglobin levels by 20–30 g/L when taken daily for 8–12 weeks, with a slow rise in iron stores, as measured by serum ferritin levels.[13,14] Persistence of response in iron stores should be confirmed by repeat testing after a few months.

Gastrointestinal adverse effects, including abdominal pain, constipation, diarrhoea and nausea, occur in 20–50% of patients who take oral iron supplements. These adverse effects are likely dose-related and occur less often with daily doses under 60 mg of elemental iron, or with intermittent rather than daily dosing.[15,16]

Intravenous iron

Multiple intravenous iron formulations, including ferric carboxymaltose, ferric derisomaltose (also known as iron isomaltoside), iron polymaltose and iron sucrose, are available in Australia. Intravenous iron therapy allows rapid replacement of iron stores, especially in the presence of anaemia and severe iron deficiency. An improvement in haemoglobin level by 20–30 g/L over 8–12 weeks is typically seen.[13,17]

- **Ferric carboxymaltose** can be given in doses of up to 1 g in a single infusion over 15 minutes.
- **Ferric derisomaltose (iron isomaltoside)** can be administered in doses up to 20 mg/kg, to a maximum of 1.5 g, in a single infusion over 20–30 minutes.
- **Iron polymaltose** is administered in doses of up to 2.5 g in an extended infusion over 4–5 hours, with the safety of a more rapid infusion protocol of 73 minutes having been shown.[18]
- **Iron sucrose** is restricted to administration of up to 300 mg in a single infusion.

These formulations have been shown to have a favourable safety profile compared with high-molecular-weight iron dextran, which was used until the 1990s in Australia.

Infusion-associated adverse effects, including headache, flu-like symptoms, arthralgias and myalgias, occur in 10–40% of patients during or up to 2 weeks after intravenous iron administration. Infusion reactions are uncommon, but Fishbane-type reactions, comprising flushing, chest tightness and dyspnoea, may occur. These are thought to be a manifestation of non-allergic complement activation-related reactions rather than allergic hypersensitivity.[19] Mild to moderate infusion reactions may be more common with certain iron formulations, occurring in 8.7% of patients who received ferric derisomaltose compared with 2.1% of patients who received ferric carboxymaltose in one study.[20] Staining at the cannula site, if not sited properly, can be permanent.

Hypophosphataemia has been documented after administration of intravenous iron, typically with a nadir at 1–2 weeks. The risk of hypophosphataemia is higher with ferric carboxymaltose (40–70%) than with other formulations.[17,21-24] Although this is transient and asymptomatic in most patients, it may be persistent and severe in a small proportion of patients. Cases of persistent hypophosphataemia with osteomalacia and fractures have been described, mostly after repeated infusions of ferric carboxymaltose.[25]

The dose of intravenous iron is typically based on the simplified dosing algorithm (Box 1). The Ganzoni formula has been used for calculating the dose of iron polymaltose and iron sucrose (Box 2).[21]

1 Simplified dosing algorithm for intravenous iron

	Bodyweight*	
Haemoglobin	35 to < 70 kg	≥ 70 kg
< 100 g/L	1500 mg	2000 mg
≥ 100 g/L	1000 mg	1500 mg

* Use ideal bodyweight in overweight patients. If patient is underweight, use actual bodyweight.

2 Ganzoni formula

Total iron dose (mg iron) = bodyweight (kg) × (target haemoglobin – actual haemoglobin [g/L]) × 0.24 + depot iron need (mg iron)*

* For bodyweight < 35 kg, depot iron need is 15 mg/kg bodyweight; for bodyweight ≥ 35 kg, depot iron need is 500 mg.

9. Prevention

Primary prevention

A nutritious diet with sufficient iron intake to prevent iron deficiency is recommended, depending on age, sex and pregnancy status, as outlined above. People at greater risk of iron deficiency because of physiological, nutritional or social factors may require higher dietary iron intake. Additional oral or intravenous iron therapy is only recommended after evaluation of circulating iron studies.

Secondary prevention

Once detected, iron deficiency should be corrected using oral or intravenous iron therapy. The underlying cause of iron deficiency should be evaluated and treated as required to prevent recurrence of iron deficiency. Repeat evaluation of circulating iron studies after 3–4 months is important to detect adequate increment in iron stores or recurrence of iron deficiency. Dietary iron intake should be optimised, which may require formal dietetic consultation.

10. References

1. Kassebaum NJ, Jasrasaria R, Naghavi M, et al. A systematic analysis of global anemia burden from 1990 to 2010. *Blood* 2014; 123: 615-624.

2. Karr M, Alperstein G, Causer J, et al. Iron status and anaemia in preschool children in Sydney. *Aust N Z J Public Health* 1996; 20: 618-622.

3. Stoltzfus RJ. Iron deficiency: global prevalence and consequences. *Food Nutr Bull* 2003; 24 (4 Suppl): S99-S103.

4. Lopez A, Cacoub P, Macdougall IC, et al. Iron deficiency anaemia. *Lancet* 2016; 387: 907-916.

5. Karr MA, Mira M, Alperstein G, et al. Iron deficiency in Australian-born children of Arabic background in central Sydney. *Med J Aust* 2001; 174: 165-168.

6. Mast AE, Blinder MA, Gronowski AM, et al. Clinical utility of the soluble transferrin receptor and comparison with serum ferritin in several populations. *Clin Chem* 1998; 44: 45-51.

7. Rizvi S, Schoen RE. Supplementation with oral vs. intravenous iron for anemia with IBD or gastrointestinal bleeding: is oral iron getting a bad rap? *Am J Gastroenterol* 2011; 106: 1872-1879.

8. National Health and Medical Research Council. *Nutrient reference values for Australia and New Zealand including recommended dietary intakes*. Version 1.2. Canberra: NHMRC, 2006.

9. Kohgo Y, Ikuta K, Ohtake T, et al. Body iron metabolism and pathophysiology of iron overload. *Int J Hematol* 2008; 88: 7-15.

10. Oustamanolakis P, Koutroubakis IE, Messaritakis I, et al. Soluble transferrin receptor-ferritin index in the evaluation of anemia in inflammatory bowel disease: a case-control study. *Ann Gastroenterol* 2011; 24: 108-114.

11. Skikne BS, Punnonen K, Caldron PH, et al. Improved differential diagnosis of anemia of chronic disease and iron deficiency anemia: a prospective multicenter evaluation of soluble transferrin receptor and the sTfR/log ferritin index. *Am J Hematol* 2011; 86: 923-927.

12. Patterson AJ, Brown WJ, Roberts DC, et al. Dietary treatment of iron deficiency in women of childbearing age. *Am J Clin Nutr* 2001; 74: 650-656.

13. Kulnigg S, Stoinov S, Simanenkov V, et al. A novel intravenous iron formulation for treatment of anemia in inflammatory bowel disease: the ferric carboxymaltose (FERINJECT) randomized controlled trial. *Am J Gastroenterol* 2008; 103: 1182-1192.

14. Gasche C, Ahmad T, Tulassay Z, et al. Ferric maltol is effective in correcting iron deficiency anemia in patients with inflammatory bowel disease: results from a phase-3 clinical trial program. *Inflamm Bowel Dis* 2015; 21: 579-588.

15. Low MS, Speedy J, Styles CE, et al. Daily iron supplementation for improving anaemia, iron status and health in menstruating women. *Cochrane Database Syst Rev* 2016; (4): CD009747.

16. Fernandez-Gaxiola AC, De-Regil LM. Intermittent iron supplementation for reducing anaemia and its associated impairments in adolescent and adult menstruating women. *Cochrane Database Syst Rev* 2019; (1): CD009218.

17. Reinisch W, Staun M, Tandon RK, et al. A randomized, open-label, non-inferiority study of intravenous iron isomaltoside 1,000 (Monofer) compared with oral iron for treatment of anemia in IBD (PROCEED). *Am J Gastroenterol* 2013; 108: 1877-1888.

18. Garg M, Morrison G, Friedman A, et al. A rapid infusion protocol is safe for total dose iron polymaltose: time for change. *Intern Med J* 2011; 41: 548-554.

19. Auerbach M, Henry D, DeLoughery TG. Intravenous ferric derisomaltose for the treatment of iron deficiency anemia. *Am J Hematol* 2021; 96: 727-734.

20. Mulder MB, van den Hoek HL, Birnieet E, et al. Comparison of hypersensitivity reactions of intravenous iron: iron isomaltoside-1000 (Monofer®) versus ferric carboxy-maltose (Ferinject®). A single center, cohort study. *Br J Clin Pharmacol* 2019; 85: 385-392.

21. Evstatiev R, Marteau P, Tariq T, et al. FERGIcor, a randomized controlled trial on ferric carboxymaltose for iron deficiency anemia in inflammatory bowel disease. *Gastroenterology* 2011; 141: 846-853.

22. Wolf M, Koch TA, Bregman DB. Effects of iron deficiency anemia and its treatment on fibroblast growth factor 23 and phosphate homeostasis in women. *J Bone Miner Res* 2013; 28: 1793-1803.

23. Bishay RH, Ganda K, Seibel MJ. Long-term iron polymaltose infusions associated with hypophosphataemic osteomalacia: a report of two cases and review of the literature. *Ther Adv Endocrinol Metab* 2017; 8: 14-19.

24. Fang W, Kenny R, Rizvi QUA, et al. Hypophosphataemia after ferric carboxymaltose is unrelated to symptoms, intestinal inflammation or vitamin D status. *BMC Gastroenterol* 2020; 20: 183.

25. Schaefer B, Wurtinger P, Finkenstedt A, et al. Choice of high-dose intravenous iron preparation determines hypophosphatemia risk. *PLoS One* 2016; 11: e0167146.