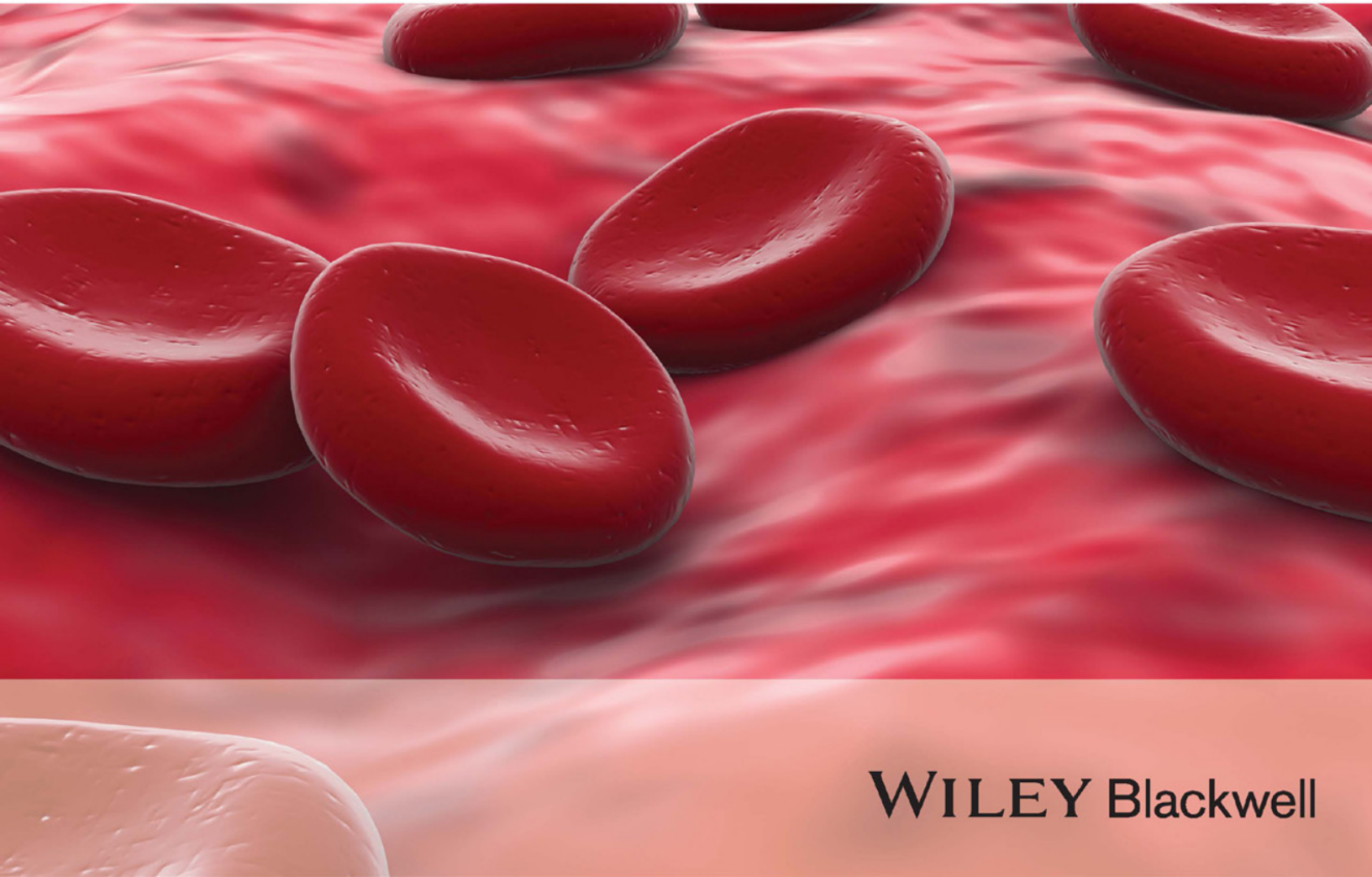
ABC of Clinical Haematology

Fifth Edition

Edited by Drew Provan and Claire Harrison



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WILEY Blackwell

This fifth edition first published 2023

Edition History
John Wiley & Sons Ltd (1e, 1997; 2e, 2003; 3e, 2007; 4e, 2018)

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John Wiley & Sons, Inc., 111 River Street, Hoboken, NJ 07030, USA
John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK

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Library of Congress Cataloging-in-Publication Data applied for

Paperback ISBN: 9781119890744

Cover image: Wiley
Cover design by © rzdeb/Getty Images

Set in 9.25/12pt Minion by Straive, Pondicherry, India

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Preface to the Fifth Edition

Haematology has changed hugely in the four years that have elapsed since the fourth edition of the *ABC of Clinical Haematology* was published. Advances in basic sciences, molecular biology, and therapeutics have led to greater understanding of haematological diseases and provided much-needed treatments for many malignant and non-malignant disorders.

As editors, we felt that the *ABC of Clinical Haematology* required a major overhaul because there have been significant advances in all disease areas, particularly cellular therapies, myeloma, acute leukaemias and non-malignant disorders of red cells, platelets and bleeding. We have worked with many new authors who have rewritten much of the book, and these revised chapters now reflect modern practice and have brought the book totally up to date. For the first time, we have incorporated a chapter on paediatric haematology, making the book useful to an even wider audience, including medical students, nurses, family doctors and other health professionals involved in the care of adults and children with haematological diseases.

The quality of any book depends on the writing. We are immensely grateful to our colleagues who have contributed valuable chapters despite the pressures of heavy clinical workloads and recent events, which have made things even more stressful.

We are grateful for the project management and support from the team at Wiley, in particular Sophie Bradwell, associate editor; Katherine King, associate managing editor; Tiffany Taylor, copy editor; and many others who have helped us reshape the book and complete the project. We are delighted with the final product, and we sincerely hope readers enjoy the book.

As with all publications, errors can creep in, and we would be happy to hear from readers if any major errors or omissions are found.

Drew Provan (a.b.provan@qmul.ac.uk)
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February 2023

CHAPTER 1

Iron Deficiency Anaemia

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OVERVIEW

- Iron deficiency is the commonest cause of anaemia worldwide and is frequently seen in general practice.
- The anaemia of iron deficiency is caused by defective synthesis of haemoglobin, resulting in red cells that are smaller than normal (microcytic) and contain reduced amounts of haemoglobin (hypochromic).

Iron metabolism

Iron has a pivotal role in many metabolic processes, and the average adult contains 3–5 g of iron, of which two-thirds is in the oxygen-carrying molecule haemoglobin (Hb).

A normal Western diet provides about 15 mg of iron daily, of which 5–10% is absorbed (~1 mg), principally in the duodenum and upper jejunum, where the acidic conditions help the absorption of iron in the ferrous form. Absorption is helped by the presence of other reducing substances, such as hydrochloric acid and ascorbic acid. The body has the capacity to increase its iron absorption in the face of increased demand – for example, in pregnancy, lactation, growth spurts and iron deficiency (Table 1.1).

Once absorbed from the bowel, iron is transported across the mucosal cell to the blood, where it is carried by the protein transferrin to developing red cells in the bone marrow. Iron stores comprise ferritin, a labile and readily accessible source of iron, and haemosiderin, an insoluble form found predominantly in macrophages.

About 1 mg of iron a day is lost from the body in urine, faeces, sweat and cells shed from the skin and gastrointestinal tract. Menstrual losses of an additional 20 mg a month and the increased requirements of pregnancy (500–1000 mg) contribute to the higher incidence of iron deficiency in women of reproductive age (Box 1.1).

Table 1.1 Daily dietary iron requirements.

Male	1 mg
Adolescence	2–3 mg
Female (reproductive age)	2–3 mg
Pregnancy	3–4 mg
Infancy	1 mg
Maximum bioavailability from normal diet (about)	4 mg

Clinical features of iron deficiency

The symptoms accompanying iron deficiency depend on how rapidly the anaemia develops. In cases of chronic, slow blood loss, the body adapts to the increasing anaemia, and patients can often tolerate extremely low concentrations of haemoglobin – for example, <70 g/l – with remarkably few symptoms. Most patients complain of increasing lethargy and dyspnoea. More unusual symptoms are headaches, tinnitus, taste disturbance and restless leg syndrome. Pica (a desire to eat non-food substances) and, most characteristically, pagophagia (abnormal consumption of ice) are uncommon but well-described and resolve promptly with iron replacement. In children, chronic iron deficiency anaemia can lead to impaired psychomotor and cognitive development.

On examination, several skin, nail, hair and other epithelial changes may be seen in chronic iron deficiency. Atrophy of the skin occurs in about a third of patients, and hair thinning may be particularly noted in young women. Nails may become brittle, but the classic finding of koilonychia (spoon-shaped nails) is unlikely to be seen in clinical practice in higher-income countries. Patients may also complain of angular stomatitis, in which painful cracks appear at the angle of the mouth, sometimes accompanied by glossitis. Although uncommon, oesophageal and pharyngeal webs can be a feature of iron deficiency anaemia (consider this in middle-aged women presenting with dysphagia). These changes are believed to be due to a reduction in the iron-containing enzymes in the epithelium and gastrointestinal tract. Few of these epithelial changes are seen in modern practice and are of limited diagnostic value.

Tachycardia and cardiac failure may occur with severe anaemia irrespective of cause, and in such cases, prompt remedial action should be taken.

When iron deficiency is confirmed, a full clinical history, including leading questions on possible gastrointestinal blood loss

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Box 1.1 **Causes of iron deficiency anaemia.**

Most iron deficiency anaemia is the result of blood loss, especially in affluent countries.

Blood loss	Increased demand	Poor intake
Reproductive system Menorrhagia	Growth spurts Pregnancy, lactation Patients with chronic renal failure undergoing haemodialysis and receiving erythropoietin	**Malabsorption** Coeliac disease Atrophic gastritis (also may result *from* iron deficiency) Infection: Helicobacter pylori, tropical sprue Post-surgical: Gastric bypass, small bowel resection **Dietary** Vegans Elderly Infants under 12 months fed predominantly on cow's milk
Gastrointestinal tract Oesophagitis Oesophageal varices Hiatus hernia (ulcerated) Peptic ulcer Inflammatory bowel disease Haemorrhoids (rarely) Carcinoma: stomach, colorectal Angiodysplasia Hereditary haemorrhagic telangiectasia (rare) Parasitic infection (e.g. hookworm/ strongyloides) – commonest cause of iron deficiency worldwide		
Renal tract Carcinoma (especially bladder) Schistosoma haematobium infection Intravascular haemolysis with renal haemosiderin excretion		
Iatrogenic Multiple blood sampling (especially premature infants) Blood or platelet donation		

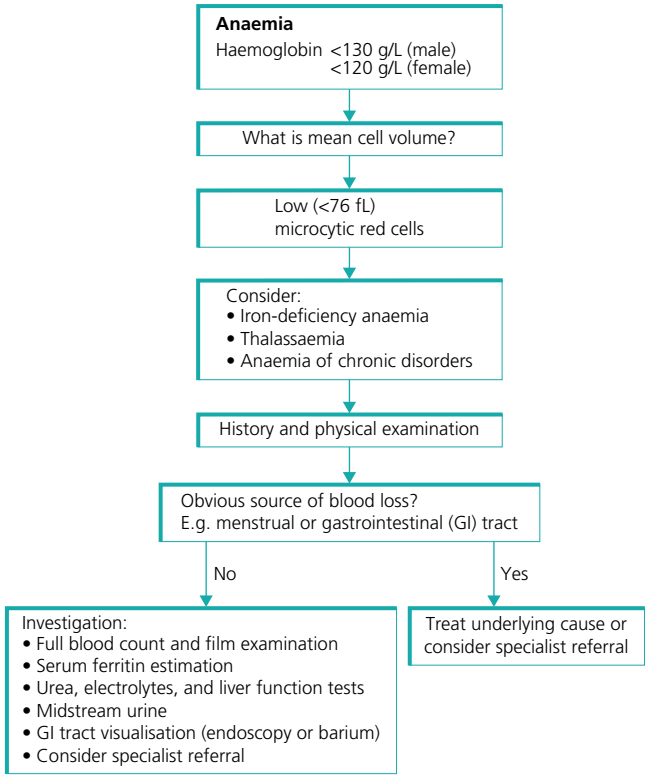

Figure 1.1 Diagnosis and investigation of iron-deficiency anaemia.

or malabsorption (as in, for example, coeliac disease), should be obtained. Menstrual losses should be assessed, and the importance of dietary factors and regular blood donation should not be overlooked (Figure 1.1).

Diet alone is seldom the sole cause of iron deficiency anaemia in adults in Britain except when it prevents an adequate response to a physiological challenge – as in pregnancy, for example. In children, by contrast, diet is a key factor, particularly in infants slow to wean (e.g. by 6 months) or those fed cow's milk (which has low iron content and poor bioavailability) before 12 months.

A state of 'functional iron deficiency' is common in patients with chronic inflammatory conditions and often co-exists with anaemia of chronic disease. Total body iron may be normal, but iron stores cannot be mobilized for making new red cells due to changes in metabolic or transport pathways.

Laboratory investigations

A full blood count and film should be assessed (Box 1.2). These will confirm the anaemia, and recognising the indices of iron deficiency is usually straightforward (reduced haemoglobin concentration, reduced mean cell volume (MCV), reduced mean cell haemoglobin (MCH), reduced mean cell haemoglobin concentration). It is worth noting that a reduction in haemoglobin concentration is a *late* feature of iron deficiency, and in up to 40% of cases, MCV may be normal. The first change may be an increase in the red cell distribution width. There may be a reactive thrombocytosis. Some modern analysers will determine the percentage of hypochromic red cells or the haemoglobin content of reticulocytes, both of which reflect the availability of iron for making new red cells. The blood film shows

Box 1.2 **Investigations in iron deficiency anaemia.**

- Full clinical history and physical examination
- Full blood count and blood film examination
- Haematinic assays (serum ferritin, iron studies, vitamin B_{12}, folate)
- % hypochromic red cells and reticulocyte Hb content (if available and diagnosis is uncertain)
- Urea and electrolytes, liver function tests
- Coeliac serology
- Urinalysis
- Fibreoptic and/or CT imaging studies of the gastrointestinal tract
- Pelvic ultrasound (females, if indicated)

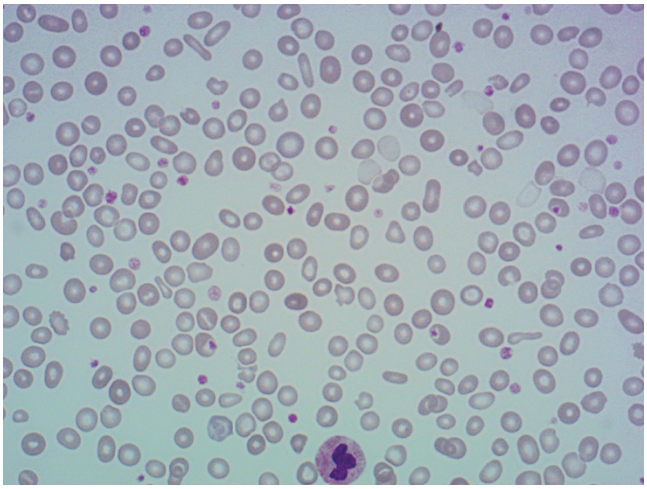

Figure 1.2 Blood film showing changes from iron-deficiency anaemia.

Table 1.2 Diagnosis of iron deficiency anaemia.

Haemoglobin	**Men <130 g/l, women <120 g/l**
MCV	Reduced*
MCH	Reduced*
MCHC	Reduced*
Blood film	Microcytic hypochromic red cells with pencil cells and target cells
Serum ferritin	<15 μg/l most specific <30 μg/l likely iron deficient
Transferrin saturation	≤15% strongly supportive <20% suggestive of iron deficiency
% hypochromic red cells	Elevated (>5%)
Reticulocyte mean Hb	Reduced (<29 pg)

* Check with local laboratory for reference ranges.
MCH, mean cell haemoglobin; MCHC, mean cell haemoglobin concentration; MCV, mean cell volume.

microcytic hypochromic red cells, pencil cells and occasional target cells (Figure 1.2, Table 1.2).

Hypochromic anaemia occurs in other disorders, such as anaemia of chronic disease and sideroblastic anaemias and in globin synthesis disorders, such as thalassaemia. Difficulties in diagnosis arise when more than one type of anaemia is present – for example, iron deficiency and folate deficiency in malabsorption, in a population where thalassaemia is present, or in pregnancy, when the interpretation of red cell indices may be difficult. To help confirm iron deficiency, further haematinic assays are used (Table 1.3).

The haematinic measure of choice is serum ferritin, reduced levels (especially <15 μg/l) being highly specific for iron deficiency. However, its sensitivity is limited, in part because as an acute phase protein, the concentration may be normal or even raised in inflammatory or malignant disease. A prime example of this is found in rheumatoid disease, in which active disease may result in a spuriously raised serum ferritin concentration masking an underlying iron deficiency caused by gastrointestinal bleeding after non-steroidal analgesic treatment. There may also be confusion in liver disease as the liver contains stores of ferritin that are released after hepatocellular damage, leading to raised serum ferritin concentrations.

Table 1.3 Characteristics of anaemia associated with other disorders.

	Iron deficiency	**Chronic disease**	**Thalassaemia trait (α or β)**	**Sideroblastic anaemia**
Degree of anaemia	Any	Seldom <90 g/l	Mild	Any
MCV	↓	N or ↓	↓↓	N or ↓ or ↑
Serum ferritin	↓	N or ↑	N	↑
Transferrin/TIBC	↑	N or ↓	N	N or ↓
Transferrin saturation	↓	N or ↓	N	↑
Marrow iron	Absent	Present	Present	Present

MCV, mean cell volume; N, normal; TIBC, total iron binding capacity.

In cases where ferritin estimation is likely to be misleading, iron studies may aid the diagnosis. Serum iron levels alone are unhelpful due to wide diurnal variation. Levels of transferrin rise in iron deficiency, as does total iron binding capacity (TIBC). Transferrin saturation is calculated as serum iron/transferrin concentration ×100 and reflects the proportion of transferrin molecules occupied by iron. A value less than 15–20% is suggestive of iron deficiency. Levels of iron-binding proteins can also be influenced by other factors such as acute inflammation, malnutrition, pregnancy or drugs, including the oral contraceptive pill, while transferrin saturation is subject to diurnal variation and is affected by recent oral intake. In complex cases, diagnosis of iron deficiency requires combining all available tests and clinical information, and where doubt remains, a therapeutic trial of iron might be warranted.

Diagnostic bone marrow sampling is seldom performed in simple iron deficiency, but if the diagnosis is in doubt, a marrow aspirate may be carried out to demonstrate absent bone marrow stores (Figure 1.3).

When iron deficiency has been diagnosed, the underlying cause should be investigated and treated. Often the history will indicate

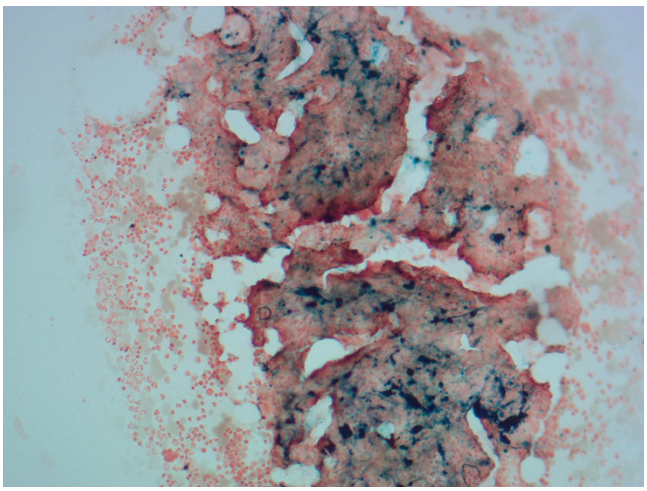

Figure 1.3 Bone marrow aspirate stained with Prussian blue showing adequate iron stores in the marrow.

the likely source of bleeding – for example, menstrual blood loss or gastrointestinal bleeding. If there is no obvious cause, further investigation generally depends on the age and sex of the patient. Coeliac serology should be sent even if the patient has no gastrointestinal symptoms, as coeliac disease may present with iron deficiency alone. In male patients and postmenopausal women, possible gastrointestinal blood loss is investigated by visualisation of the gastrointestinal tract via endoscopy (upper and lower). A 'virtual' CT colonoscopy is an alternative in frail patients. It may occasionally be necessary to proceed to a wireless capsule investigation of the small bowel if endoscopies are normal and clinical suspicion remains high.

Management

Effective management of iron deficiency relies on (a) the appropriate management of the underlying cause (for example, gastrointestinal or menstrual blood loss) and (b) iron replacement therapy.

Oral iron replacement therapy with gradual replenishment of iron stores and restoration of haemoglobin is the preferred treatment (Table 1.4). Oral ferrous salts are the treatment of choice (ferric salts are less well absorbed) and include ferrous sulphate, ferrous gluconate and ferrous fumarate. All three compounds are associated with a high incidence of side effects, including nausea, constipation and diarrhoea. These side effects may be reduced by taking the tablets after meals and with vitamin C, but even milder symptoms account for poor compliance with oral iron supplementation. Interrupted dosing, such as one tablet on alternate days or 3 days per week, can be as effective whilst causing fewer side effects.

Effective iron replacement therapy should result in a rise in haemoglobin concentration of around 1 g/l per day (about 20 g/l every 3 weeks), with a response seen within 5 to 7 days, but this varies from patient to patient. Once the haemoglobin concentration is within the normal range, iron replacement should continue for three months to replenish the iron stores.

Failure to respond to oral iron therapy

The main reason for failure to respond to oral iron therapy is poor compliance. However, if the losses (for example, bleeding) exceed the amount of iron absorbed daily, the haemoglobin concentration will not rise as expected; this will also be the case in combined deficiency states.

The presence of underlying inflammation or malignancy may also lead to a poor response to therapy. Occasionally, malabsorption of iron such as that seen in coeliac disease may lead to a failure to respond. High levels of dietary phytates (bran, oats, rye), polyphenols (tea) and calcium may impair absorption of iron if taken together, and patients should avoid these an hour either side of taking iron. Finally, an incorrect diagnosis of iron deficiency anaemia should be considered in patients who fail to respond adequately to iron replacement therapy.

Table 1.4 Elemental iron content of various oral iron preparations.

Preparation	Amount (mg)	Ferrous iron (mg)
Ferrous sulphate	200	65
Ferrous gluconate	300	35
Ferrous fumarate	210	65–70

Intravenous iron preparations

Parenteral iron may be used when the patient cannot tolerate oral supplements – for example, when patients have severe gastrointestinal side effects or if the losses exceed the daily amount that can be absorbed orally. Patients on renal dialysis receiving erythropoietin also routinely require intravenous iron, and some patients with anaemia of chronic disease and functional iron deficiency may see an improvement in haemoglobin following iron given intravenously.

Intravenous iron should be given under strict medical supervision – for example, on a haematology day unit – due to the risk (although small) of anaphylaxis or other reactions. Full resuscitation facilities must be available. Preparations include Venofer and Ferinject, given in several divided doses, and CosmoFer and Monofer, which can be administered as a single total-dose infusion (Box 1.3, Figure 1.4).

The dose is based on the estimated iron deficit, calculated using the Ganzoni formula (Box 1.4). In practice, fixed-dose regimes are often used, or quick reference tables are available, giving the dose for the patient's weight and target versus actual haemoglobin level. A peak response to intravenous iron can usually be expected within 4–6 weeks.

Alternative treatments

Blood transfusion is not indicated unless the patient has decompensated due to a drop in haemoglobin concentration and needs a more rapid rise in haemoglobin – for example, in cases of

Box 1.3 **Intravenous iron preparations.**

Compound	Trade name	Elemental iron concentration (mg/ml)	Administration
Iron hydroxide dextran	CosmoFer	50	Total dose infusion (max 20 mg iron/kg body weight)
Iron isomaltoside	Monofer	100	Total dose infusion (max 20 mg iron/kg body weight)
Iron sucrose	Venofer	20	Max dose 200 mg iron, up to three times per week
Ferric carboxymaltose	Ferinject	50	Max dose 1000 mg iron, once per week

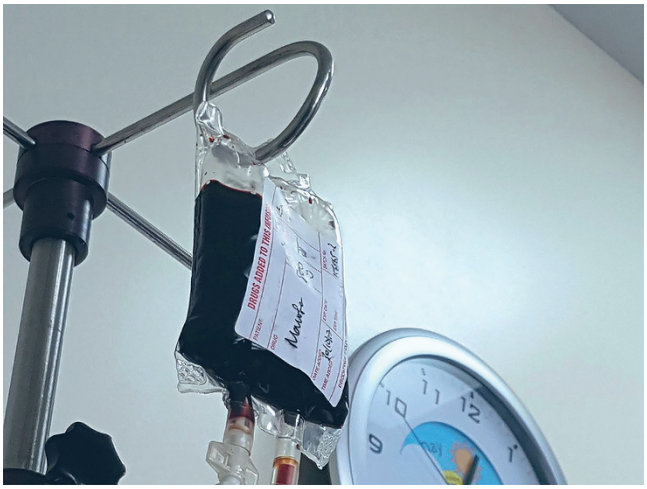

Figure 1.4 Intravenous iron infusion. This is usually given on a day ward under medical supervision.

Box 1.4 **Iron dose calculation.**

Total dose = Body weight (kg) × [Target Hb – Actual Hb] (g/L) × 0.24* + 500 mg for iron stores

* Where 0.24 = Percentage blood volume by weight (7%) × Iron content of Hb (0.34%) × 1000 (g to mg conversion)

worsening angina or severe coexisting pulmonary disease. In cases of iron deficiency with serious ongoing acute bleeding, blood transfusion may be required.

Prevention

When absorption from the diet is likely to be matched or exceeded by losses, extra sources of iron should be considered – for example, prophylactic iron supplements in pregnancy or after gastrectomy, or encouragement of breastfeeding or use of formula milk rather than cow's milk during the first year of life. All patients at risk of iron deficiency should be given advice on good sources of dietary iron (Box 1.5).

Box 1.5 **Iron content of some iron-rich foods.**

Food	Iron per 100 g
Animal-based	
Beef/lamb	2–3.5 mg
Pork chop/sausages	0.7–1.1 mg
Chicken	0.7 mg
White fish	0.5 mg
Prawns/tuna (canned)	1 mg
Eggs	2.2 mg
Plant-based	
Pulses (chickpeas, kidney beans, baked beans, lentils)	1.4–2 mg
Tofu	1.2 mg
Nuts (almonds, hazelnuts, brazil nuts, peanut butter)	2–3 mg
Seeds (sesame, sunflower)	6–10 mg
Dried fruit (apricots, figs, dates)	3–4 mg
Green vegetables (spinach, broccoli)	1–1.5 mg
Fortified breakfast cereal	8–12 mg

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