ARTICLE

Correcting iron deficiency

SUMMARY

Iron deficiency is the most common cause of anaemia. It has many different causes, so further investigations are required to establish an underlying aetiology.

An iron study is the first-line investigation and includes serum iron, ferritin, transferrin and transferrin saturation. Serum ferritin is normally a suitable indicator of iron stores but can be increased by inflammation to an extent that makes the ferritin unreliable for assessment of iron deficiency.

Oral iron replacement is the most appropriate first-line treatment in the majority of patients. Its efficacy can be limited by poor patient compliance due to the high rate of gastrointestinal adverse effects and the prolonged treatment course needed to replenish body iron stores.

Intravenous iron preparations are indicated when oral iron therapy has failed or rapid replenishment is required.

Ferric carboxymaltose can rapidly deliver a large dose of iron, making it the preparation of choice for outpatients.

Despite their excellent safety profiles, all intravenous iron preparations carry the risk of anaphylaxis. Patients require monitoring and access to resuscitation facilities.

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Introduction

In 2010, the global prevalence of anaemia was 32.9% and iron deficiency was the most common cause.[1] There are few population studies examining the prevalence of iron deficiency and epidemiological data can be methodologically flawed as anaemia is usually ascribed to iron deficiency.[2] Using anaemia as an indirect indicator, it can be estimated that most preschool children and women in non-industrialised countries and a significant proportion in industrialised countries are iron deficient.

In Australia the prevalence of iron deficiency varies depending on the study population. It affects approximately 10% of non-pregnant young women, and is estimated to be highly prevalent in indigenous communities.[3] Other at-risk groups for iron deficiency include the very young and the very old, and people with restrictive dietary patterns such as vegetarians and vegans.

Iron deficiency

Iron plays a key role in multiple metabolic pathways including respiration, energy production, DNA synthesis and cell proliferation. The clinical consequences of untreated iron deficiency are diverse. They include fatigue, exacerbations of certain diseases such as angina, neurobehavioural disorders such as restless leg syndrome,[4] and cognitive impairment in children.[5]

Iron deficiency can be due to multiple underlying causes (Table 1) and patients should be investigated according to guidelines to determine the underlying aetiology. The Gastroenterological Society of Australia has produced guidelines regarding appropriate investigation for patients with iron deficiency. Iron deficiency can be subdivided into:

- **absolute iron deficiency** due to insufficient iron stores
- **functional iron deficiency**, when demand from increased erythropoiesis temporarily outstrips supply
- **sequestration**, when existing iron stores are sufficient but become unavailable. Sequestration is usually a consequence of proinflammatory disease states such as chronic kidney disease, autoimmunity, infections and malignancy. Iron replacement is not required and is potentially harmful.

These mechanisms are not mutually exclusive.[6]

Assessing iron stores

An iron study is the investigation of choice in assessing iron stores. It measures serum iron, transferrin, transferrin saturation, total iron-binding capacity and ferritin. The Gastroenterological Society of Australia guidelines specify fasting iron studies, as dietary intake can affect serum iron concentrations. However as clinical decisions are rarely made on

Table 1 **Causes of iron deficiency**

Cause	Example
Physiological	
• increased demand	Infancy, rapid growth, pregnancy, menstrual blood loss
Environmental	Insufficient intake e.g. vegan diet
Pathological	
• decreased absorption	Gastrectomy, duodenal bypass, Crohn's disease
• chronic blood loss	Gastrointestinal tract – peptic ulcer disease, colorectal cancer, angiodysplasia Systemic bleeding – postoperative, recent trauma
Drug related	Non-steroidal anti-inflammatory drugs, proton pump inhibitors, glucocorticoids
Genetic	Iron-refractory iron deficiency anaemia

Table 2 **Interpreting iron profile results according to aetiology and severity**

	Anaemia of chronic disease	Iron deficiency without anaemia	Severe iron deficiency with anaemia
Serum iron	↓	↓	↓
Serum transferrin or serum total iron binding capacity	↓ or low normal	↑ or high normal	↑
Serum transferrin saturation (%)	↓	↓	↓
Serum ferritin	↑ or high normal	↓	↓
Blood film	Normal	Normal	Hypochromia and microcytosis

Box 1 **Dietary sources of iron**

Heme iron

Liver
Red meat
Seafood
Poultry

Non-heme iron

Beans
Dark green leafy vegetables
Dried fruit, raisins and apricots
Iron-fortified bread, cereal, pasta

this parameter alone, many people do not routinely follow these recommendations.[7] Among the iron studies, serum ferritin is the most sensitive and specific test for evaluating a patient's iron stores.[8] A serum ferritin of less than 30 microgram/L is diagnostic of iron deficiency and should prompt investigation for an underlying cause (see Fig.) and appropriate treatment.[9]

Transferrin is a protein that transports iron and reflects total iron-binding capacity. A transferrin saturation of less than 16% indicates an iron supply that is insufficient to support normal erythropoiesis.

Diagnosing iron deficiency can be challenging as ferritin is also an acute-phase protein, which can be elevated in the presence of infections, autoimmunity, chronic kidney disease and certain malignancies. In these scenarios ferritin can potentially overestimate the patient's iron stores. Serum ferritin up to 300 microgram/L can still be compatible with iron deficiency in the presence of inflammation and needs to be interpreted with other parameters measured in the iron profile and supportive red-cell indices such as mean corpuscular volume and a blood film (Table 2). Depending on the clinical urgency, it may be better to recheck the iron profile once the acute illness has settled before commencing replacement.

Assessing bone marrow iron stores with Prussian Blue staining is still considered the gold-standard investigation. However, this invasive investigation is rarely required for confirming iron deficiency.

Correcting iron deficiency

There are multiple strategies for correcting iron deficiency ranging from dietary advice to blood transfusion. The choice will be influenced by the severity of anaemia and the comorbidities of the patient.

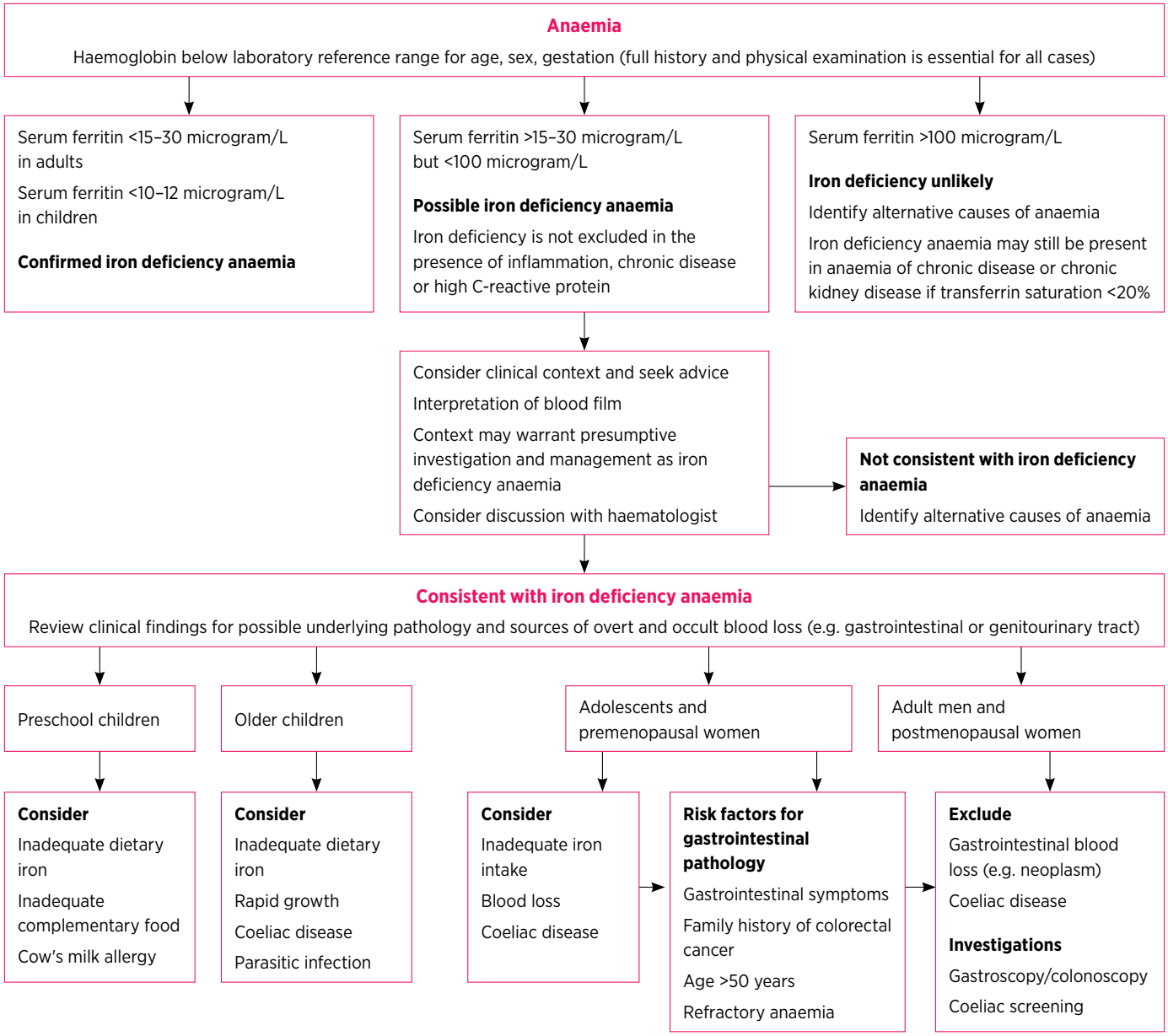
Diet

It is imperative to ensure that the patient has an adequate iron intake, particularly if they have a restrictive diet such as veganism. In general, plant iron is non-heme iron (Box 1) which is poorly absorbed, however co-ingestion of an antioxidant such as vitamin C (e.g. a glass of orange juice) may improve absorption.

Oral iron

Oral iron therapy should correct anaemia and replenish iron stores. Therapeutic Guidelines suggests ferrous sulfate at a dose of 325–650 mg daily (equivalent to 105–210 mg elemental iron), however other guidelines recommend higher doses.[10] There are no comparative trials evaluating effectiveness or tolerability. Ferrous fumarate and gluconate salts

Fig. **Investigation of iron deficiency**



are equally effective in practice. Vitamin C enhances iron absorption[11] and is compounded with several iron preparations (Table 3).

Patients should be advised to take oral iron supplementation on an empty stomach as phosphates, phytates and tannates in food bind iron and impair absorption. Patients should also be advised to take iron either two hours before or four hours after the ingestion of antacids.

While there are obvious advantages to oral iron supplements such as cost, safety and ease of access, there are also several limitations. Adverse effects such as constipation, dysgeusia and nausea reduce adherence,[12] and hence effectiveness, particularly when the recommended duration of therapy is 3–6 months. Poor adherence is a common cause for failure to respond to oral iron therapy, however other causes should also be considered (Table 4).

Liquid iron replacement can be trialled in patients intolerant of iron tablets. It can be taken in divided daily doses reducing gastrointestinal adverse effects, however it can discolour teeth.

Table 3 **Oral iron preparations**

Brand name	Formulation	Elemental iron content
Ferro-gradumet	Ferrous sulfate 325 mg Controlled-release tablets	105 mg
Ferrograd C	Ferrous sulfate 325 mg Vitamin C 500 mg Controlled-release tablets	105 mg
FGF	Ferrous sulfate 250 mg Folic acid 300 microgram Controlled-release tablets	80 mg
Fefol	Ferrous sulfate 270 mg Folic acid 300 microgram Controlled-release capsules	87 mg
Ferro-F-tab	Ferrous fumarate 310 mg Folic acid 350 microgram Non-controlled-release tablets	100 mg
Ferro-tab	Ferrous fumarate 200 mg	65.7 mg
Ferro-liquid	Ferrous sulfate 30 mg/mL	6 mg/mL

Table 4 **Reasons for failure to respond to oral iron therapy**

Reason	Example
Inadequate iron intake	Non-adherence, insufficient iron content in supplement
Inadequate iron absorption	Concomitant consumption of inhibitors of iron absorption (e.g. tea, calcium) Coexisting inflammation with iron sequestration Intestinal mucosal disorders (e.g. coeliac disease) *Helicobacter pylori* infection Impaired gastric acid secretion (use of proton pump inhibitors)
Ongoing blood losses	Occult blood loss
Coexisting condition interfering with bone marrow response	Concomitant vitamin B_{12} or folate deficiency, primary bone marrow disease
Incorrect diagnosis	Haemoglobinopathy, anaemia of chronic disease or renal failure

Liposomal oral iron preparations are currently under evaluation.[3,13] These consist of iron encased in a phospholipid coat containing ascorbic acid, which prevents direct contact between iron and the intestinal mucosa thereby reducing gastrointestinal adverse effects.

Iron is toxic in overdose. It is therefore important to store oral iron products out of reach of children.

Parenteral iron

Parenteral iron is indicated when oral therapy has failed or when patients require rapid iron replacement. Intramuscular injections of formulations such as iron polymaltose are painful and can permanently stain the skin and should be avoided where possible. Intravenous infusion results in a rapid replenishment of iron stores with peak ferritin concentrations at 7–9 days after infusion.[14] In our experience the haemoglobin should rise within 2–3 weeks in the majority of patients. There are several intravenous iron preparations available in Australia (Table 5).

Ferric carboxymaltose

Ferric carboxymaltose is the preferred formulation in ambulatory settings, such as Hospital in the Home services and suitably equipped general practices, as it can deliver up to 1 g of iron in 15 minutes and has an excellent safety profile. It is superior to oral

iron in increasing serum ferritin and haemoglobin in the management of postpartum iron deficiency[15] and correcting preoperative anaemia.[16] Compared to placebo it alleviates the symptoms of heart failure,[17] and ferric carboxymaltose is non-inferior to ferrous sulfate in inflammatory bowel disease.[18]

The REPAIR-IDA trial was the largest randomised trial comparing ferric carboxymaltose to iron sucrose in patients with non-dialysis-dependent chronic kidney disease. The study demonstrated that ferric carboxymaltose was safe, effective and required fewer doses making it potentially more cost-effective than iron sucrose.[19] Other studies have also found favourable cost-effectiveness.[20]

One limitation is ferric carboxymaltose can only be infused in doses up to 1 g per week. It therefore cannot always provide the amount of iron required according to the Ganzoni formula (see Box 2). Two infusions at least one week apart may be needed.

Iron polymaltose

Iron polymaltose may be the preferred intravenous iron preparation for inpatients as a larger dose of iron can be infused in a single sitting. However, there are several logistical limitations such as preparation time (the case illustrating the Ganzoni formula would require 19 ampoules) and the lengthy duration of administration of up to five hours that requires frequent observations. This limits its use outside of hospital.

Iron sucrose

The use of iron sucrose is restricted by the Pharmaceutical Benefits Scheme to patients on chronic intermittent haemodialysis. It is more effective at improving haematocrit and ferritin than ferric chloride.[21]

Safety of intravenous iron

Hypersensitivity reactions, which can be fatal, can occur with all intravenous iron formulations[22] and the patient should be aware of this when giving consent. This risk is substantially lower with non-dextran formulations such as ferric carboxymaltose, iron polymaltose and iron sucrose. The estimated risk of serious anaphylactic reactions with ferric carboxymaltose is 0.1%. The European Medicines Agency recommended that all intravenous iron preparations should only be given in an environment where resuscitation facilities are available.[23]

Box 3 shows the common adverse effects associated with iron infusions. Infusion site reactions, such as pain, extravasation and injection site discolouration, occur at a rate of approximately 1.6% with ferric carboxymaltose. This is comparable to other intravenous iron formulations.

Table 5 **Intravenous iron preparations**

Compound	Maximum single dose	Duration of infusion
Ferric carboxymaltose (Ferinject)	1000 mg Repeat a week later	Up to 15 minutes depending on dose
Iron polymaltose (Ferrosig)	1000–2500 mg	Approximately 5 hours
Iron sucrose (Venofer)	100 mg during dialysis 3 times per week	15 minutes minimum

Box 2 **Ganzoni formula**

Total iron dose (mg iron) =
Body weight (kg) x (Target – Actual haemoglobin) (g/L)* x 0.24 + Iron for iron stores (mg iron)**

* Haemoglobin must be in g/L

** Iron stores

<35 kg body weight = 15 mg/kg body weight

>35 kg body weight = 500 mg

Example: 80 kg female with a haemoglobin of 80 g/L needs a dose of 80 x (150–80) x 0.24 + 500 = 1844 mg iron

Box 3 **Adverse effects of intravenous iron preparations**

Immediate adverse effects

Headache
Nausea
Vomiting
Dysgeusia
Arthralgia
Myalgia

Anaphylactoid

Wheezing
Flushing
Dyspnoea
Dizziness

Infusion site reactions

Localised pain
Discolouration of skin

Delayed adverse effects (1–2 days post infusion)

Mild fever
Headache
Arthralgia
Myalgia

REPAIR-IDA[19] reported a higher incidence of mild adverse events in patients treated with ferric carboxymaltose compared to iron sucrose. These included mild hypersensitivity reactions, nausea and flushing, however there was no statistically significant difference on the pre-specified safety end points. REPAIR-IDA did report an increase in the number of hypertensive episodes and hypophosphataemia with ferric carboxymaltose compared to iron sucrose.

This raised concerns regarding the safety of this formulation in patients with a high cardiovascular risk. However, subsequent meta-analysis has confirmed the safety of ferric carboxymaltose[24] and a recent prospective study has shown that ferric carboxymaltose reduces the risk of hospitalisations in patients with heart failure compared to placebo.[25] A recent meta-analysis has not reported an increased risk of serious infections with use of intravenous iron preparations.[24]

Conclusion

Iron deficiency anaemia is a common clinical problem that has a diverse range of causes and mandates further investigations to establish an aetiology. An iron study is a key investigation and serum ferritin is the most sensitive component. However, the ferritin concentration is affected by the presence of inflammation so a careful assessment of other results such as mean corpuscular volume and a blood film is required.

There are a number of oral iron preparations, however these are often poorly tolerated, limiting their effectiveness. Liquid iron replacement allows divided daily doses and reduces adverse effects. New liposomal preparations are under evaluation.

Intravenous iron should be considered as second-line therapy for patients who do not respond to oral iron or require rapid iron replacement. Ferric carboxymaltose is a non-dextran intravenous iron formulation that can deliver a large dose of iron in a short time. It has been evaluated in a number of patient populations and has been shown to be safe and effective. Ferric carboxymaltose is preferred to iron polymaltose for outpatients as it is easier to manage. ◀

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