

Iron Deficiency



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Acknowledgements Expert Advisers

Prof. Jane Andrews
A/Prof. Don Cameron
Prof. Finlay Macrae
Dr. Sue Shepherd
Prof. Simone Strasser

Medical Writer

Ms. Mary Sinclair

The document has been prepared by the Digestive Health Foundation of the Gastroenterological Society of Australia and every care has been taken in its development. The document is intended to be used as a guide only and not an authoritative statement of every conceivable step or circumstance which may or could relate to the management of iron deficiency.

Clinicians should use this document as an aid in relation to **iron deficiency** and not as a complete authoritative statement. Medical understanding of **iron deficiency** is evolving. This document reflects this understanding as at October 2015 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 +/- 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 GI assessment and consideration of upper and lower GI endoscopy UNLESS there is a history of obvious, recent significant non-GI blood loss. This entails good clinical judgment; however, serious gastrointestinal pathology as the cause of iron deficiency should always be considered. For those interested in a greater level of detail, the British Society of Gastroenterology has recent guidelines.¹⁵

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1 Overview

According to the World Health Organisation, iron deficiency is the most common nutritional deficiency worldwide, with as many as 80% of the world's population iron deficient, while 30% may have iron deficiency anaemia. It is not only widespread in children and women in developing countries but it is the only nutrient deficiency which remains prevalent in almost all industrialised nations.¹

Iron deficiency is common in Australia² Depletion of iron stores and iron deficiency occur in all age groups, particularly in groups of the population such as children, women after the onset of menstruation, elderly people, vegetarians (especially vegans), and in disadvantaged populations such as Indigenous Australians, refugees, recent migrants^{3,4,5} and institutionalised people. Iron deficiency and anaemia are not synonymous terms. Iron deficiency is only one cause of anaemia, and in the early stages of iron deficiency, anaemia is not present.

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 in circulating erythrocytes and another quarter in readily metabolised stores as ferritin or haemosiderin in the liver and reticulo-endothelial system. The remaining iron is in the myoglobin of muscle tissue and a variety of enzymes necessary for oxidative metabolism and other cell functions.^{2,6}

Iron deficiency develops gradually and is generally minimally symptomatic until anaemia develops. Deficiency results when iron requirements are not met by iron absorption from the diet. The three common situations leading to this imbalance are:

- excess iron loss (bleeding)
- inadequate dietary iron intake
- malabsorption of iron due to disease of the small intestine.

Iron deficiency usually begins with an iron imbalance (iron needs are inadequately met by iron absorption) that depletes the storage form of iron while the blood haemoglobin level, a marker of iron status, remains normal.

After storage iron is depleted, however, there is inadequate iron for normal haematopoiesis and iron-deficiency anaemia (an advanced stage of iron depletion) develops.⁷

Iron intake and its absorption can vary widely, depending on dietary and environmental factors.⁸

Recommended Dietary Intake (RDI) Of Iron (mg/day)

Age	Male	Female	Pregnancy
0-6 months	0.2	0.2	
7-12 months	11	11	
1-3 years		9	
4-8 years	10	10	
9-13 years	8	8	
14-18 years	11	15	27
19-50 years	8	18	27
> 51 years	8	8	

Source: Australian National Health and Medical Research Council (NHMRC) and the New Zealand Ministry of Health (MoH). Nutrient Reference Values for Australia and New Zealand Including Recommended Dietary Intakes 2006.
<https://www.nrv.gov.au/nutrients/iron>

The clinical consequences of iron deficiency are both haematological (due to anaemia) as well as non-haematological (deficiency of iron-containing cellular enzymes in muscle and brain especially) such as decreased aerobic work performance, developmental delay, cognitive and intellectual impairment, adverse pregnancy outcome and impaired immune function.⁷

Once identified, iron deficiency can be easily and successfully corrected, but an underlying cause must always be sought and treated because iron deficiency is never an end diagnosis in itself.

People with iron deficiency may have inadequate dietary intake, impaired absorption, or blood loss which can be either known or occult.

Both overt and occult blood loss resulting in iron deficiency are frequently due to gastrointestinal disease; investigation of the gut should always be considered in patients with iron deficiency.

Even in those patients with one obvious cause of iron deficiency, the possibility of another serious underlying cause must also be considered. Therefore, the treatment and investigation of iron deficiency are parallel strands of clinical care: both need to be dealt with concurrently.

Given the role of the gut in both absorption and loss of iron, the specialities of gastroenterology is pivotal in the responsibility for the appropriate diagnosis and treatment of iron deficiency with or without anaemia.

2 DEFINITIONS

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

Iron deficiency: The state of too little iron in the body. The term iron deficiency does not indicate the severity of deficiency; other terms are used to stratify the degree of deficiency (see box). The early stages of deficiency are associated only with decreased storage iron, whereas the later stages of iron deficiency lead to the development of anaemia.

Anaemia: Blood haemoglobin levels are below normal. Also evidenced by low haematocrit, and low packed cell volume (which assess red cell mass and thus are indirect measures of haemoglobin levels).

Iron deficiency anaemia: An advanced stage of iron depletion; anaemia due to iron deficiency (as iron is essential for formation of haemoglobin, and thus red cells).

Iron status: The current state of iron balance in an individual. There is a continuum from iron deficiency with anaemia, to iron deficiency with no anaemia, to normal iron status with varying amounts of stored iron and finally to iron overload, which can cause organ damage when severe.¹

Iron deficiency without anaemia is three times as common as iron-deficiency anaemia.⁹ It should again be noted that not all anaemias are secondary to iron deficiency.

Definitions of iron status³

Iron replete: males: haemoglobin > 135 g/L; females: > 115 g/L, and serum ferritin > 30 µg/L

Iron depletion: low iron stores (ferritin < 15- 30 µg/L) but no change in haematological parameters

Iron deficiency: low iron stores (ferritin < 15µg/L) and reduced mean red corpuscular volume (MCV) (< 80 fL) but normal haemoglobin concentration (serum ferritin < 15 µg/L ; or serum ferritin 15-20 µg/L, plus two of the following: serum iron < 10 µmol/L; total iron binding-capacity > 68 µmol/L; serum transferrin > 3.5 g/L or transferrin saturation < 15%)

Iron-deficiency anaemia: low iron stores, reduced mean red corpuscular volume and reduced haemoglobin concentration.

<https://www.rcpa.edu.au/getattachment/c047c27e-c67a-470f-bb6b-e4084de22d97/Interpreting-Serum-Ferritin.aspx>

The terms iron deficiency, iron deficiency anaemia and anaemia are often used interchangeably but they are not the same.

Key messages

- Iron deficiency is common in the community
- Iron deficiency may be present with or without anaemia
- Anaemia indicates more severe and usually longer duration of iron deficiency
- Iron deficiency may indicate serious disease
- Iron deficiency is never a final diagnosis in itself
- A cause of iron deficiency should always be sought
- While seeking a cause, the iron deficiency itself should be corrected

3 CLINICAL CONSEQUENCES AND SYMPTOMS OF IRON DEFICIENCY

Iron deficiency can cause¹⁰:

- decreased memory and other mental changes (impaired learning and concentration are particularly important in children)
- impaired immune function
- decreased aerobic sports performance
- fatigue that impairs the ability to do physical work in adults
- adverse pregnancy outcomes, both for mother and baby
- infant developmental delay (both motor and mental function).

In addition, there is growing evidence of an association between iron deficiency and obesity in children¹¹. Children with iron deficiency have also been shown to have more severe symptoms of attention-deficit hyperactivity disorder (ADHD) than those without iron deficiency, consistent with its effect on mental function in unaffected children.

Iron deficiency is usually minimally symptomatic until iron-deficiency anaemia occurs. However, this does not mean that iron deficiency is not important to treat. It is important to screen for iron status among high-risk groups and to recognise signs of iron deficiency in all at-risk patients.

Symptoms which may suggest iron deficiency include:

- fatigue, feeling tired, listless and weak;
- decreased exercise capacity;
- decreased work and school performance;
- decreased concentration capacity;
- decreased libido;
- difficulty maintaining body temperature;
- decreased immune function (with consequent increased susceptibility to infection);
- glossitis; and/or
- pica or geophagia.

Iron-deficient infants can be lethargic, listless, irritable and anorexic.

4 RISK GROUPS

Those most at risk of iron deficiency in Australia:

- Pregnant women because of rapid foetal growth and higher iron needs.
- Adolescent girls and women of childbearing age because of menstruation (especially those with heavy menstrual loss).
- Young children because of rapid growth and inadequate iron intake.
- Children with chronic disease or restricted diets.
- People on restricted diets, in particular, vegetarians and vegans (poor absorption of non-haem iron).
- People with chronic renal failure on haemodialysis as they have regular loss of blood (iron) in establishing dialysis through the lines.¹²
- Institutionalised or socially disadvantaged people, including:
 - elderly people in residential care
 - Indigenous Australians
 - displaced people
 - refugees
 - migrants from economically poor countries
 - people in tropical countries who are frequently subject to hookworm
 - hospitalised patients
 - (dietary inadequacy; problems with Dentition and swallowing;
- possible long-term or recurrent intestinal infections).
- People with undiagnosed/untreated coeliac disease.¹³
- People with chronic gastrointestinal blood loss from aspirin or other non-steroidal anti-inflammatory drug (NSAID) use, angioectatic lesions, peptic ulcer disease, ulcerative oesophagitis, undiagnosed colorectal, oesophageal or gastric cancer, or inflammatory bowel disease.
- Athletes (elite level).
- People who have had weight loss surgery, especially where bypass of normal anatomy has been undertaken - as iron is only absorbed in the very proximal small bowel.

Adult men and post-menopausal 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, such as aspirin or other NSAID-related erosions and ulcers, angioectasia, advanced colonic polyps and gastrointestinal malignancy (colorectal most common). Both upper and lower gastrointestinal endoscopy are usually necessary. Iron deficiency can be the ONLY manifestation of gastrointestinal diagnoses including of cancer.

5 CAUSES OF IRON DEFICIENCY

Iron deficiency has many causes. Even when an obvious cause of iron deficiency is recognised (such as low dietary intake), the possibility of another serious underlying cause should be considered.⁸

Iron deficiency develops in three ways.^{7,10}

Excessive blood loss

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

In men and post-menopausal women, the most likely causes of chronic blood loss include upper gastrointestinal erosions or ulcers related to aspirin or other NSAID use, gastrointestinal angiodysplasia or dysplasia, colonic polyps and bowel cancer.

Other situations causing blood loss may be regular blood donation, unexpectedly large peri-operative blood loss, salicylate/ NSAID enteropathy and some less common gastrointestinal conditions such as inflammatory bowel disease (Crohn's disease or ulcerative colitis) or chronic enteric infection with parasites such as hookworms.

Inadequate iron intake in the diet

Red meat is the principal source of dietary iron in most Australian diets. Red meat has high concentrations of iron in an easily absorbable form. In order to obtain the RDI for iron, red meat (60 - 100 g) should be consumed at least three times each week.¹⁴ Despite the apparent plentiful supply of dietary iron in Australia, many people develop iron deficiency from an inadequate dietary intake.

Reasons for low dietary intake include:

- food preferences (more white meat or fish intake, with little or no red meat)
- poor dietary knowledge (unawareness of better absorption of haem compared with non-haem iron)
- social disadvantage (cost and knowledge of food preparation) voluntary dietary restriction (vegetarian, vegan).

Inadequate iron absorption by the gut

Iron absorption is the amount of dietary iron that the body absorbs from food sources. Iron absorption is regulated such that it increases when body stores are low and decreases when iron stores are high to prevent toxic effects of iron overload.⁷

Causes of inadequate iron absorption by the gut include:

- undiagnosed/untreated coeliac disease (damaged/reduced small intestinal absorptive surface)
- inadequate dietary haem iron intake (see above)
- gastric surgery, including obesity surgery (banding or bypass)
- achlorhydria from extensive gastric atrophy (usually only seen if dietary intake is also marginal)
- rarely, down-regulation of iron absorption in Crohn's disease and other chronic diseases.
- other less common malabsorptive conditions (such as Whipple's disease, tropical sprue and ulcerative jejunoileitis)

Iron absorption also depends on the type of dietary iron consumed. Food provides iron in two forms: haem and non-haem. Haem iron is present in animal foods and is absorbed four to five times more easily than non-haem iron, which is found in plant foods such as rice, maize, black beans, soybeans and wheat. The difference in absorption rates of haem and non-haem iron accounts for the increased frequency of iron deficiency in those who eat little, or no, red meat (e.g. vegetarians, especially vegans).

Rich sources of haem iron include red meats (beef, lamb, veal, pork), and to a lesser extent, other meats such as poultry and fish. The redder the meat, the higher the iron content. Organ meats (liver, kidney) and foods made from these (e.g. pate) are also rich sources of haem iron.

Rich sources of non-haem iron include eggs, nuts, wholemeal pasta and bread, iron-fortified breakfast cereal, dried beans and lentils, and leafy green vegetables (e.g. spinach, silver beet, broccoli).

Factors that enhance non-haem iron absorption

- The absorption of non-haem iron foods is three times greater when taken with haem iron foods
- Vitamin C also enhances absorption of non-haem iron. Vitamin C-rich foods include citrus fruits and juices, strawberries, kiwi fruit, papaw, melons, green leafy vegetables, tomatoes and capsicum
- Organic acids such as malic, citric and ascorbic acids commonly found in vegetables can also enhance the absorption of non-haem iron.

Factors that reduce iron absorption

- Natural compounds found in plants such as phytates (found in cereals and legumes), phosphates (found in eggs), polyphenols (found in red wine), tannins (found in tea and coffee) and some proteins found in soybeans can bind to iron and limit absorption. When iron intake is marginal, it is therefore recommended to drink tea and coffee between meals.
- Calcium-rich foods and calcium supplements can inhibit the absorption of both haem and non-haem iron in foods.

If daily iron intake is marginal, it is important to include foods that increase non-haem iron absorption, especially when:

- iron losses are high (heavy menstruation)
- iron requirements are high (pregnancy, lactation, childhood) only non-haem sources of iron are eaten (vegetarians, vegans).

6 ASSESSMENT OF IRON DEFICIENCY

Clinical assessment

- Identification of at-risk patients.
- History: diet, age, menses (women), social, cultural, physiological, medication and pre-existing conditions.

Diagnosis of iron deficiency

Laboratory investigation of asymptomatic iron deficiency should be based on clinical suspicion and not only on whether anaemia is present. In routine clinical practice, no single blood test is used to diagnose iron deficiency.

Iron deficiency should be suspected whenever there is a complaint of fatigue, particularly recent onset of fatigue in an at-risk patient. Additionally, it should be looked for if there is anaemia, low MCV or low mean corpuscular haemoglobin (MCH) or MCH concentration (MCHC) on a blood count. Fasting morning iron studies are the best tests to diagnose iron status, providing serum iron, ferritin, transferrin (or total iron binding capacity [TIBC]) and transferrin saturation.

Although the most common tests (more available, less expensive) are haemoglobin concentration and haematocrit value, these measures are not usually decreased until late stages of iron deficiency (anaemia).

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

Investigation of iron status

Biochemical tests detect earlier changes in iron status. The serum markers typical of iron deficiency are:^{10,15}

- low ferritin;
- low serum iron;
- raised total transferrin or TIBC;
- decreased transferrin saturation.

Concurrent disease, particularly inflammatory disease, can falsely elevate ferritin and make it less reliable, whereas a low ferritin is always diagnostic of iron deficiency. When inflammation is present, iron deficiency should still be suspected unless the ferritin is >200. A transferrin saturation <16% is also helpful in inflammatory states in ruling against iron deficiency.

Serum ferritin is the best single diagnostic test for iron deficiency. A ferritin concentration below 15 µg /L for adults and 12 µg /L for children is diagnostic of iron deficiency, regardless of the presence of co-existent disease. For this reason, serum ferritin is often used alone in population screening studies for the estimation of the prevalence of iron deficiency.

Ferritins between 15-20 (in children) and 15-30 in adults) should be considered as suggestive of low iron stores and may also warrant further clinical enquiry, especially regarding diet and menstrual status.

However, it is rarely used alone in clinical practice as many people at risk of iron deficiency may also have inflammatory conditions which may cause elevations in ferritin unrelated to iron status, as it is an acute phase reactant.

As ferritin is an acute phase reactant; it is often higher than 12-15 µg /L in patients with:

- concurrent acute or chronic inflammation
- malignancy
- hepatic disease
- kidney disease.

In the setting of intercurrent illness with a raised ferritin, elevated transferrin and decreased transferrin saturation still indicate iron deficiency. However, iron studies may be difficult to interpret in the presence of an elevated ferritin. Considering the transferrin saturation, as above, is useful however in rare cases, more specialised tests such as red cell protoporphyrin, transferrin binding receptors or even bone marrow biopsy may be required to distinguish between iron deficiency and anaemia of chronic disease. Where the iron studies are unclear, advice from a haematologist should be sought.

Never simply treat people with iron without confirming they have iron deficiency. Patients with persistently elevated serum ferritin levels, without chronic inflammatory disorder, should be tested for iron overload.

Serum ferritin concentration is the single most specific biochemical test that correlates with relative total body iron stores^{1, 16}. Reduced ferritin is the most useful indicator of iron deficiency as there is no other condition that can produce this result.

7 MANAGEMENT OF IRON DEFICIENCY

Management of iron deficiency includes two concurrent components:⁸

- the correction of iron deficiency,
- the diagnosis and treatment of the underlying disorder which lead to iron deficiency.

The urgency with which iron replacement is undertaken depends on the degree of anaemia (if present), the degree of iron deficiency and the presence of intercurrent cardiorespiratory disease (making restoration of adequate oxygen carrying capacity more urgent).

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

Where iron repletion cannot be achieved or recurs, re-referral and re-investigation should be considered, to ensure the causal lesion has not been missed.

The correction of iron deficiency may involve some or all of the following treatment:

- dietary advice;
- oral iron supplements;
- intravenous iron infusion; and less commonly,
- blood transfusion.

Once replacement has been achieved, many patients require dietary advice to ensure deficiency does not recur.

The aim of treatment should be to restore haemoglobin levels and red cell indices to normal and to replenish body stores.¹⁶

Dietary management

Addressing dietary iron intake plays a crucial role, both in the prevention of iron deficiency and in the management of early iron deficiency. Diet modifications include more iron-rich foods and positive modification of the factors influencing iron absorption.⁸

An understanding of the bioavailability of iron is essential: non-haem iron requires acid digestion and depends on the concentration of iron absorption enhancers (such as ascorbate and red meat) and iron absorption inhibitors (such as calcium, fibre, tea, coffee and wine) in the diet.

Iron supplementation

Iron supplementation is indicated when anaemia is present and more rapid restoration of iron stores is required as diet alone is unlikely to restore iron levels promptly to normal. Treatment of an underlying cause should prevent further iron loss but all patients should have iron supplementation both to correct iron deficiency and replenish body stores.

In the presence of anaemia, oral iron is recommended for three months after the haemoglobin has been corrected so that stores are replenished. Adequate replacement should be confirmed with iron studies to evaluate iron status a week or two after therapy has ceased. Persisting normal iron stores should be confirmed again a few months after repletion to ensure iron deficiency has not recurred.

Supplemental iron is available in two forms: ferrous and ferric. Ferrous iron salts (ferrous fumarate, ferrous sulphate, and ferrous gluconate) are the best absorbed forms of iron supplements.⁷

Elemental iron is the amount of iron in a supplement that is available for absorption. Commonly available iron supplements in Australia include ferrous sulphate (FGF 80 mg; Ferro-Gradumet 105 mg; and Ferrograd-C 325 mg). The usual dose is 1 tablet daily. Higher doses often lead to more gastrointestinal symptoms without an appreciable increase in the rate of iron repletion.

Note that when blood transfusion is used to correct iron deficiency anaemia, iron replacement is still required, as transfusion will not replete iron stores, and the iron deficiency will persist and anaemia will recur unless storage iron is normalized with either oral or IV replacement.

Investigation of underlying causes of iron deficiency

Iron deficiency is never a diagnosis in itself. The cause for the iron deficiency must be investigated and treated.

This will usually entail specialist gastroenterology referral for consideration & investigation of possible malabsorption or GI blood loss with upper +/- lower endoscopies as appropriate.

8 PREVENTION

Primary prevention

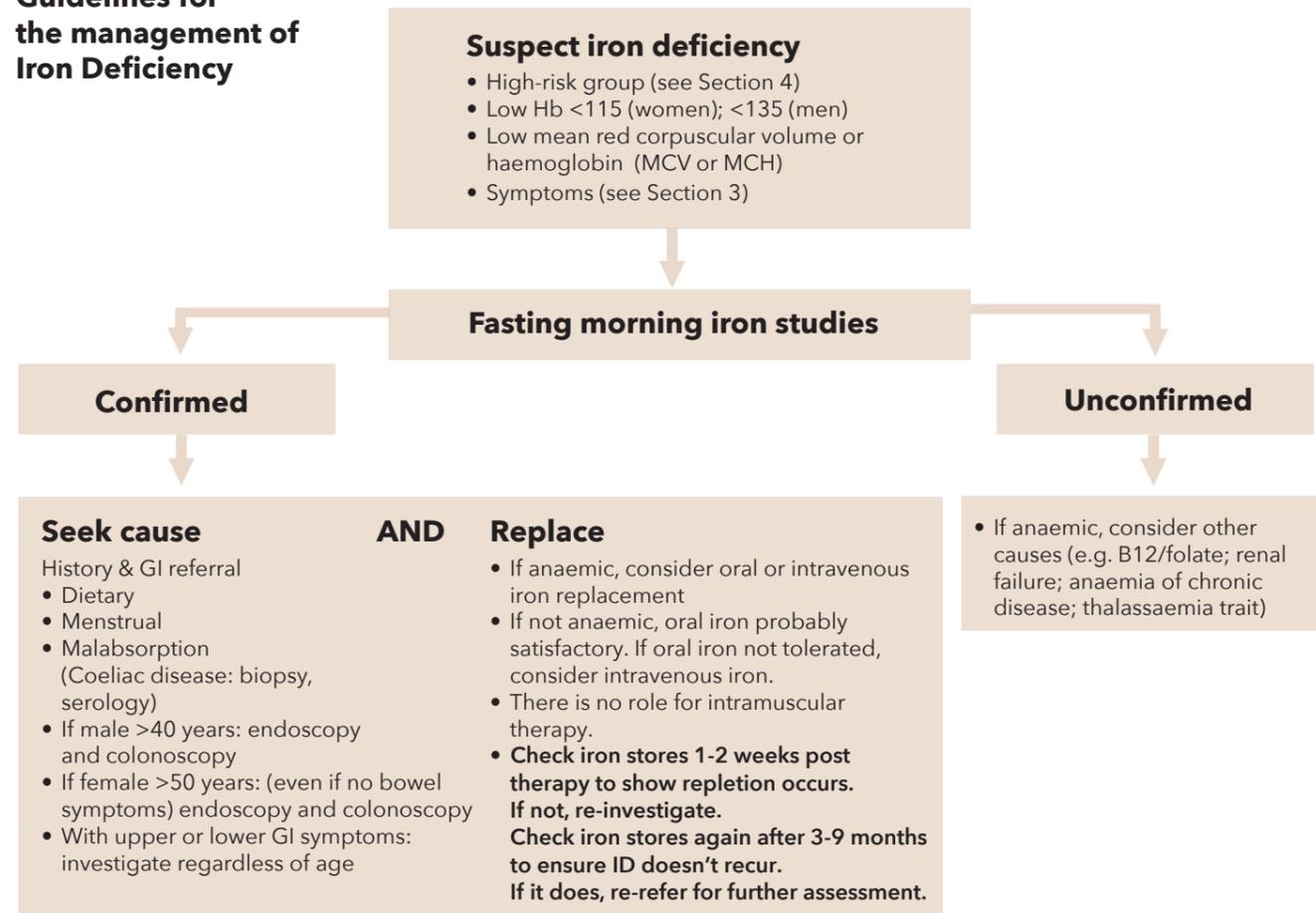
Encourage all patients to eat a diet with sufficient iron to prevent iron deficiency, especially those at risk of developing iron deficiency because of physiological, nutritional or social factors.

Secondary prevention

Screen, diagnose and treat iron deficiency. Iron deficiency detected during a routine medical examination should be corrected and fully evaluated for its cause.

9 DIAGNOSTIC AND TREATMENT ALGORITHM

Guidelines for the management of Iron Deficiency



Replacement

Oral iron

- Ferrous iron salts: Ferrous sulphate (FGF; Ferro-Gradumet; Ferrograd-C): 1 tablet daily for 60-90 days. Increasing the dose may increase the occurrence of side effects without a quicker response. Repeat fasting iron studies about 1-2 weeks after stopping therapy, to document that iron repletion has been achieved.

Intravenous iron

- Ferrum H injection: can be given as a single infusion over several hours. Dose is calculated by weight and haemoglobin (MIMS & PI)
- Ferric Carboxymaltose: Can be given IV in doses up to 1,000mg per dose over 15mins. Full iron repletion thus can usually be achieved with only 2 doses (MIMS & PI)
- Iron Sucrose can also be given in doses of 2-300mg up to 3x weekly. (Refer to pharmacist or PBS).

Failure to respond to oral iron therapy

Potential causes for failure to respond include:

- Incorrect diagnosis (e.g. thalassaemia, myelodysplastic syndrome)
- Presence of a co-existing disease interfering with response (e.g. anaemia of chronic inflammation, renal failure)
- Medication is not being taken
- Medication is not being absorbed for physical reasons (e.g. enteric coated tablets, concomitant use of antacids)
- Malabsorption of iron (untreated/undiagnosed coeliac disease, achlorhydria secondary to autoimmune atrophic gastritis or *Helicobacter pylori* infection)
- Iron (blood) loss or need is in excess of the amount ingested (e.g. ongoing GI bleeding, dialysis patient, idiopathic pulmonary haemosiderosis).

The cause for failure to respond will determine the appropriate treatment (For more information: <http://www.uptodate.com/home/index.html>)

However when failure to respond or recurrent ID occur, re-referral and reassessment with a specialist Gastroenterologist are recommended, as failure to respond may indicate a missed diagnosis.

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