Iron deficiency

How to detect it, how to correct it

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Iron deficiency and iron deficiency anaemia are common. The serum ferritin level is the most useful indicator of iron deficiency but interpretation can be complex. Identifying the cause of iron deficiency is crucial. Oral iron supplements are effective first-line treatment. Intravenous iron infusions, if required, are safe, effective and practical.

Iron deficiency and iron deficiency anaemia are common conditions that are often encountered in general practice. Iron deficiency refers to the state of reduced iron stores, whereas in iron deficiency anaemia the deficiency is severe enough to cause anaemia.[1] Iron deficiency is the most common cause of anaemia worldwide, affecting more than two billion people.[1,2] In a study of Australian blood donors, 12% of female and 1.3% of male new donors had iron deficiency, and 3.8% of all potential new donors had anaemia.[3] Our recognition of the importance of iron in health and disease has increased significantly in recent years, and new concepts have emerged. Common terms pertaining to iron deficiency are defined in Box 1.[1,4]

Even in the absence of anaemia, iron deficiency can affect cognition in people of all ages, and impair quality of life and worsen comorbid disease in adults.[5-8] Iron deficiency anaemia in pregnancy has been associated with a risk of low birthweight, prematurity and maternal morbidity.[9-11] Iron deficiency affects between 37 and 61% of patients with chronic heart failure, and its treatment can improve exercise capacity and quality of life.[12] Iron deficiency is common among people with chronic kidney disease, and correction is required to address anaemia and improve disease-specific quality of life scores.[12]

Iron deficiency and iron deficiency anaemia are therefore highly prevalent in the community and in hospital patients and are associated with considerable morbidity. This review outlines important considerations for identifying at-risk individuals and diagnosing and treating iron deficiency and iron deficiency anaemia. An algorithm for the identification and management of adults with iron deficiency is shown in the Flowchart.

How to diagnose iron deficiency

Diagnosing iron deficiency can be straightforward, but many patients have active

KEY POINTS

- Measurement of the serum ferritin level is the most useful diagnostic assay for detecting iron deficiency, but interpretation may be difficult in patients with comorbidities.
- Identifying the cause of iron deficiency is crucial; referral to a gastroenterologist is often required.
- Faecal occult blood testing is not recommended in the evaluation of iron deficiency; a negative result does not impact on the diagnostic evaluation.
- Oral iron is an effective first-line treatment, and simple strategies can facilitate patient tolerance.
- For patients who cannot tolerate oral therapy or require more rapid correction of iron deficiency, intravenous iron infusions are safe, effective and practical, given the short infusion times of available formulations.
- Intramuscular iron is no longer recommended for patients of any age.

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comorbid disease that influences laboratory test results and their interpretation. Understanding the impact of patient factors on the clinical and laboratory manifestations is important, as physiological states of increased iron requirement, chronic inflammation and disorders that impair absorption will influence both the diagnosis and management of iron deficiency.

Clinical signs and presentation

Symptoms and signs of both iron deficiency and iron deficiency anaemia include lethargy, brittle nails, hair loss and restless leg syndrome.[13-15] Pica (ingestion of non-food substances, such as soil) and pacophagia (excessive ice consumption) can occur and appear more common in women and children than in men.[15] Clinical signs of iron deficiency include atrophy of the tongue papillae, angular cheilosis and nail abnormalities such as Mees lines and koilonychia (spoon nails). However, these classic signs are not commonly seen, and patients with iron deficiency may have few signs. Even those with mild to moderate anaemia, if otherwise healthy, may have few to no symptoms except tiredness.

Identification of the underlying cause of iron deficiency is vital, and thus the clinician should be mindful of states that predispose to a negative iron balance. In addition to life stages associated with increased physiological iron requirements, any scenario that reduces ingestion or absorption of iron or increases blood loss can lead to iron deficiency. Causes of iron deficiency are listed in Box 2.

1. USEFUL DEFINITIONS[1,4]

Iron deficiency: insufficient available iron to meet the body's needs, with or without anaemia

Iron deficiency anaemia: decreased iron stores with anaemia

Iron-restricted erythropoiesis: impaired delivery of iron to erythroid precursors, regardless of the status of iron stores

Functional iron deficiency: inadequate utilisation of erythroid iron in the setting of increased demand, such as increased erythropoietic activity induced by erythropoiesis-stimulating agents

Anaemia of chronic disease: impaired production of erythrocytes in the context of chronic inflammatory states, including neoplasia, infection, autoimmune disease and chronic kidney disease (sometimes termed 'anaemia of chronic inflammation')

2. CAUSES OF IRON DEFICIENCY

Increased iron requirements
- Infancy
- Adolescence
- Pregnancy
- Erythropoiesis-stimulating agents

Decreased iron intake
- Vegetarian/vegan diet
- Malnutrition, anorexia

Decreased iron absorption
- Surgical causes: gastrectomy, duodenal bypass, bariatric surgery
- Inflammatory bowel disease, coeliac disease, atrophic gastritis, *Helicobacter pylori* infection
- Proton pump inhibitors, H_2-receptor antagonists
- Chronic kidney disease

Blood loss
- Gastrointestinal: carcinoma (stomach or colorectal), peptic ulcer, inflammatory bowel disease, diverticulosis, haemorrhoids, drug therapy (e.g. aspirin, NSAIDs, corticosteroids), oesophageal varices, hookworm, schistosomiasis, hereditary telangiectasia
- Genitourinary: menorrhagia, carcinoma of urinary tract, haemoglobinuria due to intravascular haemolysis (e.g. paroxysmal nocturnal or cold haemoglobinuria, valve haemolysis, march haemolysis)
- Acute major blood loss: surgery, trauma, postpartum haemorrhage
- Blood donation

Investigations to diagnose iron deficiency

No single test in isolation is able to identify all patients with iron deficiency. It is often necessary to consider many laboratory results and the clinical context to assess a patient's iron stores.

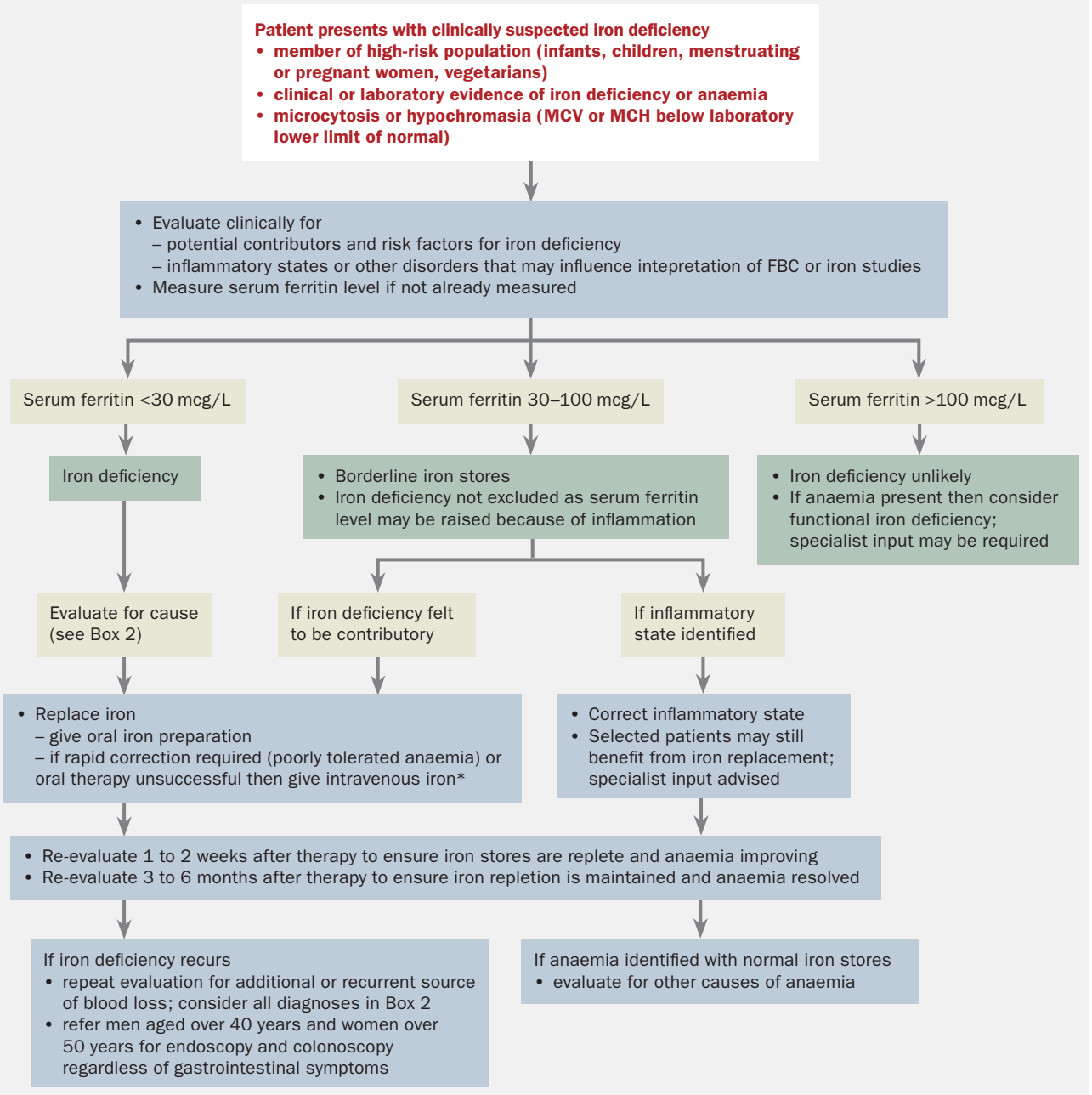
Serum ferritin and other iron studies

The serum ferritin level reflects body iron stores, and a low level confirms iron deficiency. A serum ferritin level less than 15 mcg/L (less than 12 mcg/L in children) is highly specific for iron deficiency but lacks sensitivity. The Royal College of Pathologists of Australasia recommends adopting a cut-off of 30 mcg/L, with lower levels seen as abnormal in adults.[16] Using this cut-off improves sensitivity (to 92%) and maintains an adequate positive predictive value (83%).[17] However, the serum ferritin level is difficult to interpret in patients with inflammation as it is an acute phase reactant and will therefore be elevated, making it an unreliable indicator of body iron stores in that setting. Other causes of an elevated serum ferritin level include liver disease, infection and malignancy, and assessment of iron deficiency can be challenging in patients with these conditions. A low serum ferritin level, including in patients with inflammation, confirms iron deficiency.

The remaining tests included in an iron

studies panel are less robust diagnostic tools for iron deficiency. The serum iron level indicates iron bound to transferrin and is of limited diagnostic utility because of its considerable diurnal variation, day-to-day variability and susceptibility to the effects of iron supplements and food ingestion. Consequently, the serum iron level is not used to test for iron deficiency. The total iron binding capacity (TIBC), transferrin level and transferrin saturation are markers of iron delivery to the tissues. A

AN ALGORITHM FOR THE IDENTIFICATION AND MANAGEMENT OF ADULTS WITH IRON DEFICIENCY



Abbreviations: FBC = full blood count; MCH = mean corpuscular haemogolobin; MCV = mean corpuscular volume.
* If oral iron therapy fails then also evaluate for potential causes: disease state preventing iron absorption; disease state preventing iron utilisation (functional iron deficiency); nonadherence; incorrect or additional diagnosis; or iron loss exceeding the oral dose.

transferrin saturation less than 16% is insufficient for red blood cell synthesis and thus is an accepted indicator of iron deficiency. However, the TIBC, transferrin level and transferrin saturation cannot distinguish reliably between anaemia caused by iron deficiency and by chronic inflammation.

Red blood cell parameters

A full blood count can facilitate diagnosis of iron deficiency and is required to evaluate potential anaemia. Over time, iron deficiency results in reduced mean corpuscular volume (MCV) and reduced mean corpuscular haemoglobin (MCH), manifesting as a microcytic, hypochromic blood film, with additional morphological findings of elliptocytes, including very narrow forms that may be reported as pencil cells.[18] The normal lifespan of red blood cells is three months, and therefore erythrocyte changes take time to manifest; when seen, these changes indicate that iron deficiency has been present for some time. An elevated platelet count is a common finding in patients with iron deficiency anaemia and can be due to iron deficiency or an underlying condition such as malignancy. Leukopenia and thrombocytopenia are seen in 10% of patients with iron deficiency.[18]

Red cell indices are diagnostically useful. In a healthy adult, the MCV is quite stable across time, and thus new-onset microcytosis can alert to iron deficiency or anaemia of chronic disease, whereas lifelong microcytosis may prompt consideration of an underlying haemoglobinopathy.

More recently developed red cell indices, such as reticulocyte haemoglobin content and percentage of hypochromic red cells, have been found to be potentially useful, reliable, early indicators of iron deficiency but are not in widespread clinical use.

Other investigations

An assay of soluble transferrin receptor (sTfR) was thought to offer potential as a means of distinguishing iron deficiency anaemia from anaemia of chronic inflammation. Unfortunately, the sTfR assay has a specificity of 84% and a positive predictive value of just 58% when evaluated in populations for which it would be considered most useful.[19] Furthermore, there is variability between the different sTfR assays and a lack of adequate standardisation between testing platforms. Consequently, the role of STfR in the evaluation of iron balance is more limited than expected.

Historically, the 'gold standard' test for diagnosis of iron deficiency was Perls' staining of a bone marrow aspirate. Although this test is reliable, it is rarely necessary for this indication in contemporary practice.

Evaluation of the underlying cause

It is imperative that an underlying cause of iron deficiency is rigorously explored. A thorough clinical history and examination for causes of blood loss, inadequate intake or malabsorption are required.

Men and postmenopausal women with iron deficiency require evaluation for gastrointestinal blood loss and therefore should be referred to a gastroenterologist. Faecal occult blood testing has no role in the evaluation of iron deficiency anaemia as the result, whether positive or negative, does not influence consideration of endoscopic evaluation. The need for upper or lower endoscopic evaluation will be determined by the gastroenterologist on a case by case basis.

Premenopausal women often have iron deficiency because of menstrual blood loss. A gynaecological evaluation may be required to identify causes of heavy menstrual bleeding. Endoscopic gastrointestinal evaluation should also be considered in those who are aged over 50 years or have gastrointestinal symptoms or a family history of colorectal cancer, or in whom

TABLE 1. ORAL PREPARATIONS FOR IRON REPLACEMENT

Form of iron	Presentation	Iron content	Elemental iron	Other
Tablets or capsules				
Ferrous fumarate	Tablet	310 mg	100 mg	Folic acid 350 mcg
Ferrous sulfate	Controlled release	325 mg	105 mg	Nil
Ferrous sulfate	Controlled release	325 mg	105 mg	Vitamin C 500 mg
Ferrous sulfate	Controlled release	270 mg	87 mg	Folic acid 300 mcg
Ferrous sulfate	Controlled release	250 mg	80 mg	Folic acid 300 mcg
Iron polymaltose	Tablet	370 mg	100 mg	Nil
Liquids				
Ferrous sulfate	Oral liquid	150 mg/5 mL	30 mg/5 mL	Nil
Iron polymaltose	Oral liquid	185 mg/5 mL	50 mg/5 mL	Nil

adequate oral iron therapy has failed.

Coeliac disease, autoimmune atrophic gastritis, and *Helicobacter pylori* infection are present in a considerable proportion of patients with iron-refractory iron deficiency.[20,21] Consequently, evaluation of tissue transglutaminase antibodies (suggesting coeliac disease), antiparietal and anti-intrinsic factor antibodies (autoimmune gastritis) and *H. pylori* IgG is worth considering. The diagnosis of these conditions can also be confirmed by endoscopic biopsy.

Rarely, conditions that cause chronic intravascular haemolysis can lead to iron deficiency anaemia. These include haemolysis due to mechanical heart valves, direct trauma (sometimes referred to as runners' or march haemolysis), paroxysmal nocturnal haemoglobinuria and paroxysmal cold haemoglobinuria. The remaining causes of intravascular haemolysis generally manifest more acutely, before the consequences of iron deficiency become apparent. A haemolytic screen, including assessment of a blood film, direct antiglobulin test, measurement of lactate dehydrogenase, haptoglobin, reticulocyte count and urinary haemosiderin test will help identify haemolysis. If there is concern about haemolysis then prompt haematological referral is advisable.

Rare hereditary forms of iron deficiency anaemia exist, the most common of which is termed iron-refractory iron deficiency anaemia. This is an autosomal recessive disorder that manifests with hypochromic microcytic anaemia in the presence of a normal or elevated ferritin level and thus can be confused with anaemia of chronic disease. The diagnosis and management of patients with this form of anaemia require input from a haematologist.

In summary, the cause of iron deficiency should be established and treated in parallel with the therapeutic correction of the iron deficiency. Where necessary, specialist opinion should be obtained.

Treatment of iron deficiency

Oral iron therapy

Oral iron salts, including ferrous sulfate, ferrous fumarate and iron polymaltose, are the mainstays of oral iron replacement. Oral iron is affordable, accessible and effective. Common side effects include gastrointestinal upset, manifesting as constipation, diarrhoea, abdominal cramps, dark thick stool and an altered sense of taste. These side effects are common, occurring in up to 50% of patients who trial oral iron therapy, and compromise adherence in many cases.

Provided iron deficiency anaemia does not require rapid correction, a trial of oral therapy is an appropriate first-line strategy. A standard oral dose for adults is 100 to 200 mg of elemental iron per day. Larger doses will be better tolerated if divided (e.g. 50 mg elemental iron three times daily). Currently available oral iron preparations for the treatment of iron deficiency in adults are outlined in Table 1.

Practice tips for the use of oral iron preparations are summarised in Box 3. Administration on an empty stomach allows gastric acid to assist with oral iron absorption. Administration with vitamin C can further facilitate absorption. Conversely, ingestion with tea, calcium or antacids can limit absorption. A simple strategy to ameliorate gastrointestinal side effects is to try dosing with meals; although this may compromise absorption it may facilitate adherence and thus have an overall positive effect on therapy. There is some evidence to suggest that dosing every second day is at least as effective as daily dosing and potentially more effective.[22] Thus, it is reasonable to decrease dose frequency in an effort to maximise tolerance and thus adherence. As previously mentioned, larger doses may be better tolerated if divided. If constipation occurs then an oral iron elixir is a useful option. It is worthwhile reassuring the patient that if oral therapy is not tolerated an iron infusion will be made available.

With successful oral therapy, reticulocytosis will be evident after approximately 72 hours, and a haemoglobin increment of 10 g/L every 10 days should be expected. Ensure that the patient is vitamin B_{12} and folate replete to allow rapid red blood cell production. Treatment should be continued for three to six months after normalisation of haemoglobin. Another strategy is to continue until a ferritin target level of 100 ng/mL (unaffected by inflammation) is reached to ensure repletion of iron stores.[15,23]

3. PRACTICE TIPS FOR USE OF ORAL IRON

- Counsel patients that dosing on an empty stomach with vitamin C may improve absorption
- Explain to patients that gastrointestinal side effects are common
- Educate patients about strategies to ameliorate side effects; they can try any or all of the following:
  - dose with meals
  - omit vitamin C
  - trial dosing once daily or every two days
  - dose at night so that they are asleep during the period of gastrointestinal upset
  - use an iron elixir preparation; these are occasionally tolerated by patients who cannot tolerate iron tablets because of constipation. In addition, liquid preparations allow for dose titration
- If the patient cannot tolerate oral iron despite using the above strategies then review the therapy and consider intravenous iron replacement
- If oral iron is tolerated then expect an increase in red blood cell production within a week, and a gradual progression of laboratory results towards the normal range over the following weeks (depending on the degree of iron deficiency and anaemia at commencement of replacement therapy)
- Continue oral iron therapy, provided it is tolerated, until:
  - three to six months of therapy have been completed
  - serum ferritin level is 100 ng/mL (in the absence of inflammation)
  - the cause of the iron deficiency has been addressed
- If oral iron therapy fails then consider:
  - poor adherence and intolerance
  - malabsorption – evaluate further with *Helicobacter pylori* serological testing (or urease breath test)[20]
  - persistent active disease that causes iron deficiency or inflammation

Parenteral iron therapy

Intravenous (IV) iron is a useful option for patients who are intolerant or unresponsive to oral iron therapy or require more rapid normalisation of iron stores and anaemia, such as before surgery or in the later stages of pregnancy. Additional uses of IV iron include treatment of functional iron deficiency seen in anaemia of chronic inflammation and chronic kidney disease, particularly when erythropoiesis-stimulating agents are being used.

Currently available IV iron preparations for the treatment of iron deficiency in adults are outlined in Table 2. They are safe, with low rates of serious adverse events and well-described methods for patient selection, risk minimisation and adverse event management.[15,24-26] Historically, medical education warned of the risk of iron infusions, but this was in the era of iron dextran infusions. Ferric carboxymaltose, iron polymaltose and iron sucrose have markedly lower rates of infusion reactions.[24] Headache is the most commonly reported adverse drug reaction, occurring in 3.3% of patients. Flushing and nausea reportedly occur at rates between one in 10 and one in 100, and other reactions such as fever, myalgia and arthralgia at rates between one in 100 and one in 1000.[27]

Practice tips for the use of IV iron preparations for the treatment of iron deficiency in adults are summarised in Box 4. Ferric carboxymaltose allows 1000 mg of iron to be administered within 15 minutes and thus makes outpatient administration feasible. Specialist advice should be obtained before use of IV iron in children. In adults, doses should not exceed 1000 mg per week. If more iron is required then the dose can be repeated at intervals no shorter than one week apart. Iron polymaltose and iron sucrose are alternative parenteral preparations, but ferric carboxymaltose is increasingly preferred because of its shorter infusion time.

The National Blood Authority of Australia has outlined a simplified method for calculating body iron deficit in people weighing 35 kg or over, albeit with a recommendation of caution because of limited experience with its use (Table 3).[28]

Side effects of parenteral therapy include taste alteration, nausea, headache, hypertension, arthralgia, myalgia, fever, flushing and hypersensitivity reactions. In addition, parenteral iron can result in permanent, cosmetically significant skin staining. This can occur when intravenous doses extravasate (and the dose is delivered into the soft tissue) or when the dose is given intramuscularly. It is important that this complication is mentioned during the consent process, and it further highlights the importance of appropriate monitoring during infusion therapy. Additional complications of intramuscular iron include pain and a local inflammatory response. With the availability of well-tolerated IV preparations, the role of intramuscular iron is now limited. Iron sucrose and ferric carboxymaltose should not be given intramuscularly.

Dietary advice

Diet alone is generally inadequate to replace iron stores in a patient with iron deficiency, but general dietary advice is useful to help management of patients with early iron deficiency and to prevent recurrence.[29] Patients can be guided to more iron-rich foods, both animal based and non-haem iron.

Red blood cell transfusion

Red blood cell transfusion should be reserved for patients with iron deficiency anaemia of a severity that is not tolerated by the patient. The transfusion threshold varies from patient to patient. However, if the anaemia is of gradual onset and the patient is well compensated then both oral and IV iron can generally lead to adequate haemoglobin increments without exposing the patient to transfusion-related adverse events. For example, otherwise well women of childbearing age can generally be spared the risks of transfusion, including alloimmunisation (the formation of antibodies) that may complicate future pregnancies. In the few patients who require transfusion, the aim of transfusion should be to relieve symptoms with as few units of blood as possible, rather

TABLE 2. INTRAVENOUS PREPARATIONS FOR IRON REPLACEMENT

Form of iron	Presentation	Maximum dose per administration	Dosing frequency	Rate of administration
Ferric carboxymaltose	500 mg/10 mL vial or 100 mg/2 mL vial	1000 mg (or 20 mg/kg)	Maximum dose once per week, or 200 mg three times per week	IV injection or infusion 100–200 mg: 3 minutes 200–500 mg: 6 minutes 500–1000 mg: 15 minutes
Iron polymaltose	100 mg/2 mL ampoule	2500 mg	Not applicable as entire dose can be delivered in single administration	IV infusion: first 50 mL infused slowly (20 to 40 mL/h); if tolerated then rate can be increased to 120 mL/h*
Iron sucrose	100 mg/5 mL ampoule	100 mg	Maximum three times per week	IV infusion 100 mg over 15 minutes

* Iron polymaltose can also be administered by the intramuscular route. Different maximum doses and dosing frequencies apply.

than to normalise the haemoglobin level. Iron replacement therapy remains a priority in patients who have received a transfusion, as the iron content of blood is insufficient to correct iron deficiency.

Special circumstances

Infants and children

Infants, toddlers and children are all at risk of iron deficiency, owing to their high physiological need for iron for sustained growth. There is reasonable concern about a possible association between iron deficiency in childhood and long-term adverse neurocognitive outcomes and behavioural difficulties.[30]

Treatment of infants and children

Although iron deficiency in children cannot be corrected solely by dietary change, dietary advice should be given to parents and carers. Cows' milk is low in iron compared with breast milk and infant formula, and enteropathy caused by hypersensitivity to cows' milk protein can lead to occult gastrointestinal blood loss.[31] Excess cows' milk intake (in lieu of iron-rich solid foods) is the most common cause of iron deficiency in young children.[31] Other risk factors for dietary iron deficiency include late introduction of or insufficient iron-rich foods, prolonged exclusive breastfeeding and early introduction of cows' milk.

Adult doses of iron can be toxic to children, and paediatric-specific protocols on iron supplementation should be followed. The usual paediatric oral iron dosage is 3 to 6 mg/kg elemental iron daily.[32] If oral iron is ineffective or not tolerated then consider other causes of anaemia, referral to a specialist paediatrician and use of IV iron.[32]

Pregnant women

Pregnancy places a significant demand on maternal iron stores. The increase in red blood cell mass during pregnancy, along with fetal growth, the placenta, haemorrhage and lactation increase iron requirements.[33] The maternal haemoglobin concentration declines in pregnancy because of haemodilution. The definition of a normal haemoglobin concentration in pregnancy varies between studies. However, most guidelines define anaemia in pregnancy as:

- a haemoglobin concentration less than 110 g/L in the first trimester
- a haemoglobin concentration less than 105 g/L in the second and third trimesters.[33-35]

By the third trimester, when iron requirements are maximal at 7.5 mg per day, dietary absorption is generally insufficient, and maternal stores will be used.[36] It has been shown that without supplementation, 80% of women at term have no detectable bone marrow iron stores.[37]

Recommendations about iron supplementation in pregnancy conflict. Iron supplementation in pregnancy is recommended by the US Centers for Disease Control and Prevention and the WHO.[38] However, in Australia the routine administration of iron supplements to all pregnant women is not recommended by the National Blood Authority.[39] A number of commercially available pregnancy multivitamins contain iron.

Diagnosis in pregnancy

The MCV may increase in normal pregnancy, and thus microcytosis should not be

4. PRACTICE TIPS FOR INTRAVENOUS IRON REPLACEMENT

- Check for previous allergies and pregnancy status (avoid parenteral administration in the first trimester of pregnancy)
- Ensure the facility is resourced for infusions (with resuscitation and anaphylaxis management procedures)
- Calculate body iron deficit for the individual patient
- Determine the appropriate dosing schedule depending on the agent chosen (e.g. a ferric carboxymaltose dose greater than 1000 mg should be divided appropriately)
- Administer and monitor the infusion according to product information and local standard operating procedure
- Educate the patient about signs and symptoms of hypersensitivity and other potential adverse reactions

TABLE 3. NATIONAL BLOOD AUTHORITY RECOMMENDATIONS ON CUMULATIVE IRON REQUIREMENT TO REPLETE IRON STORES[28]

Haemoglobin (g/L)	Cumulative iron requirement (mg)	
	Body weight 35 to <70 kg	Body weight ≥70 kg
<100	1500 mg	2000 mg
≥100	1000 mg	1500 mg

relied on as a marker of iron deficiency at this time. Indeed, any microcytosis in pregnancy requires prompt exclusion of underlying or coexisting haemoglobinopathy (and where relevant, paternal evaluation) to evaluate the risk of clinically significant haemoglobinopathy and hydrops fetalis. The ferritin level declines during pregnancy, to a nadir of 15 mcg/L without, and 20 mcg/L with, iron supplementation.[38]

In addition to clinical monitoring, screening for anaemia with a full blood count is recommended at the first antenatal appointment, 28 weeks of pregnancy and when there is a clinical concern about anaemia.

Treatment in pregnancy

The treatment of iron deficiency in pregnancy varies depending on its severity and the stage of pregnancy, as follows.

- Iron deficiency without anaemia can be managed with low-dose oral therapy (20 to 80 mg elemental iron per day)
- Iron deficiency anaemia in the first trimester of pregnancy should be managed with therapeutic-dose oral iron (100 to 200 mg elemental iron daily)
- Intravenous iron is recommended for:
  - women in the second or third trimester of pregnancy with moderate or severe anaemia (haemoglobin level less than 80 g/L)
  - those in whom oral therapy has failed because of poor tolerance, adherence or absorption
  - women in late pregnancy (over 34 weeks) who require more rapid haemoglobin correction.[33]

In these groups the advantages of IV iron generally outweigh the risks. Nonetheless, patients should be advised of the potential for reactions to parenteral therapy.

Intravenous iron has been found to provide a more rapid recovery from anaemia, higher haemoglobin level and better replenishment of iron stores than oral iron.[33] Furthermore, improvements in quality of life and patient-reported outcomes have also been shown.[40] The response to therapy should be assessed two weeks after the first treatment. Depending on the stage of the pregnancy and response to initial therapy, further iron can be administered if required. Postpartum anaemia is common, and some women will benefit from iron replacement after the birth. Iron stores should be reassessed approximately six weeks postpartum.

Iron deficiency, inflammation and chronic disease

Diagnosis and management of iron deficiency in the setting of inflammation and chronic disease is challenging. An expert panel has proposed that iron deficiency be diagnosed in patients with chronic heart failure, chronic kidney disease or inflammatory bowel disease if either of the following is present:[12]

- serum ferritin level less than 100 mcg/L
- total transferrin saturation less than 20%.

Australian guidelines on chronic kidney disease suggest targets for ferritin and transferrin saturation both before starting treatment with erythropoiesis-stimulating agents (ferritin more than 100 mcg/L and transferrin saturation more than 20%) and during treatment (ferritin 200 to 500 mcg/L and transferrin saturation 20 to 30%).[41]

In treating iron deficiency in patients with chronic disease or inflammation, an additional priority is to minimise the activity of the chronic or inflammatory process to restore normal iron physiology. In this context, IV iron is often required; it has been shown to be more efficacious in patients with chronic heart failure and chronic kidney disease and avoids the tolerability concerns common in patients with inflammatory bowel disease.[12]

Conclusion

Iron deficiency remains a common finding, and should alert medical practitioners to the possibility of underlying disease. Comprehensive clinical assessment and investigations are required to ensure that the patient is adequately evaluated for potential causes of iron deficiency. Parenteral iron formulations with safety profiles that permit safe outpatient infusions are now available to facilitate iron replacement, but oral replacement remains an effective first-line strategy in patients who can tolerate it. MT

References

A list of references is included in the online version of this article (www.medicinetoday.com.au).

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