

The Management of Iron Deficiency in Intestinal Failure

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Iron is the most abundant trace element in the human body and is essential for many physiological processes, including oxygen transport, energy production and DNA synthesis. The World Health Organization defines anaemia as a haemoglobin (Hb) level in men below 130 g/L, in non-pregnant women below 120 g/L, and in pregnant women below 110 g/L in the 1st and 3rd trimester and 105 g/L in the 2nd trimester. Iron deficiency anaemia (IDA) is common (30%) in patients with intestinal failure (IF) and receiving home parenteral support (HPS). In addition to general causes (e.g. reduced dietary intake and blood loss), its multifactorial causes also include malabsorption, increased losses and increased requirements.

Key points

1. The symptoms of IDA include fatigue, dyspnoea, lethargy, light-headedness, palpitations, chest pain (angina), a sore mouth and headaches. The signs include pallor, tachycardia, dry skin, angular cheilosis, brittle nails, hair loss and atrophic glossitis. Often there are no symptoms or signs, even with severe anaemia.
2. The most common reasons for IDA in non-IF patients are poor intake (e.g. vegetarian), blood loss (e.g. menorrhagia, gastrointestinal bleeding or haematuria) or coeliac disease. The investigation of IDA in IF patients starts with looking for these causes.
3. Oral intake, the length and quality of functioning in-circuit bowel affects the amount of iron needed. The exfoliation of intestinal mucosa is a cause of iron loss for some patients with IF. Intestinal iron absorption increases in iron deficiency.
4. IDA causes a microcytic anaemia (low haemoglobin [Hb] concentration and a low mean corpuscular volume); however, this may also occur in haemoglobinopathies (e.g. beta thalassaemia trait) and in copper deficiency (which can occur in IF). A low serum ferritin (which reflects iron stores) in the absence of an inflammatory process supports a diagnosis of IDA.
5. Serum ferritin may be normal in the context of anaemia with an inflammatory process (low Hb, ferritin 45-150 µg/L and a C-reactive protein [CRP] >10 g/L). In this case a serum iron, total iron binding capacity (or transferrin) and its percentage saturation, should be performed to clarify the diagnosis.
6. If a patient can take/tolerate oral medication and has functioning proximal small bowel (more than 50 cm), the treatment for IDA starts with oral iron medication (ferrous sulphate, fumarate or gluconate supplementation).
7. If oral iron is not tolerated or failing to increase the Hb level, then iron should be given intravenously (IV). Current IV iron formulations (iron dextran, iron sucrose, ferric carboxymaltose or ferric derisomaltose) have complex carbohydrate cores that bind elemental iron tightly, allowing the safe administration of full therapeutic doses in 15 to 60 minutes.
8. While anaphylactic reactions are rare with current iron preparations (except iron dextran), these medications should only be administered in a setting equipped with resuscitation facilities. Prophylactic steroids and/or antihistamines are not required.
9. Giving iron by intramuscular (IM) injection is no longer recommended due to pain, skin staining and siderosis.
10. The use of intravenous (IV) iron in acute and chronic infection is cautioned, infusions should be deferred in acute infections unless risk/benefit favours treatment.
11. The response to iron should be reviewed at 2-4 weeks. Regular ferritin measurements every 3-6 months should be made on those receiving HPS. In patients who predictably develop IDA regular iron infusions may be given prophylactically (e.g. 3-4 monthly) before the IDA redevelops.
12. Iron is present in standard trace element preparations (1.0-1.2 mg/10 ml ampoule) to meet the basic daily requirements of 1 mg/day for adult men and post-menopausal women; but is less than required by menstruating or pregnant women or those with high losses. Many patients receive too little iron as their HPS regimen may not provide daily parenteral iron. Additional iron can often be added to bespoke formulations depending on stability data.

Explanations

1. Iron is required for various cellular functions, including, but not limited to, enzymatic processes, DNA synthesis, oxygen transport and mitochondrial energy generation. As such, the symptoms of IDA can be wide ranging. Dyspnoea, fatigue, tachycardia and angina can all result from reduced blood oxygen levels. The resultant hypoxaemia can subsequently cause a compensatory decrease in intestinal blood flow, leading to dysmotility, malabsorption, abdominal pain, nausea and weight loss. Central hypoxia can cause headaches, vertigo, lethargy and cognitive impairment.

Iron deficiency can lead to fatigue and other symptoms even in the absence of anaemia. This occurs due to impaired function of the electron transport chain, a process in which iron plays a crucial role, rather than via a reduction in oxygen-carrying capacity.

2. A detailed history (including detailing current gastrointestinal anatomy) and examination should be undertaken to help detect the underlying cause of IDA, which may be multifactorial. Common causes of IDA include a poor dietary intake (e.g. vegetarian); blood loss (gastrointestinal, renal or menstrual); coeliac disease and increased requirements (e.g. pregnancy). The gastrointestinal causes include neoplasia, ulceration, inflammatory bowel disease and vascular abnormalities. Hence investigations may include an upper gastrointestinal endoscopy (with helicobacter pylori testing, gastric and duodenal biopsies), a colonoscopy (or CT colonography); urine testing for blood and coeliac antibody testing (anti-tissue transglutaminase IgA). Medications such as NSAIDs and steroids can contribute to blood loss and IDA; while medications such as proton pump inhibitors, antacids and calcium can impair iron absorption. Helicobacter pylori infection should be treated even in the absence of gastroduodenal ulceration as it can downregulate iron absorption in the duodenum.

Patient anatomy should be clarified prior to endoscopic procedures. Generally, malignancy most commonly affects the proximal colon in patients presenting with IDA; however, defunctioned intestinal (particularly colonic) segments are common in chronic IF patients. The endoscopic evaluation of segments 'out of intestinal continuity' may pose several challenges, including inadequacy of bowel preparation, technical difficulty, and significant patient discomfort. Consensus guidelines governing the investigative approach to iron deficiency anaemia in IF are lacking.

3. IF patients with a lengthy but damaged intestine due to Crohn's disease or irradiation damage may have high iron losses necessitating a greater iron requirement. Increased iron requirements may also be seen during the healing phase of an enterocutaneous fistula. Conversely, patients with a short bowel will often have lower requirements for iron due to reduced losses from desquamation. The efficiency of iron absorption increases in deficiency, and is determined by the amount of iron acquired by developing enterocytes. This regulates expression of iron transporters in the mature enterocytes of the intestinal villi, increasing their absorptive capacity.

4. A ferritin level of <15 µg/L is indicative of absent iron stores, a ferritin level of <15-30 µg/L confirms an iron deficiency, and a ferritin level of 30-45 µg/L is generally indicative of low body iron stores. Ferritin, being an acute phase response protein, can be challenging to interpret if infection or inflammation is present, becoming falsely high, even in the presence of iron deficiency. Normal ferritin levels in the presence of a raised CRP (>10 g/L) should be interpreted with caution. Other factors that may raise ferritin and mask IDA are liver disease, chronic kidney disease, malignancy and high alcohol intake. Ferritin levels are also less reliable in pregnancy.

Serum ferritin values above 150 µg/L are unlikely to occur with absolute iron deficiency, even in the presence of inflammation. In anaemia of chronic disease ferritin is raised due to an increase in the iron regulator hepcidin. Hepcidin expression is upregulated when there is infection or inflammation, via inflammatory cytokines such as IL-6. Hepcidin binds to ferroportin (the iron exporter on cells) which results in internalisation and degradation of this transporter, reducing iron release from cells.

5. When interpreting iron tests, serum iron refers to insoluble ferric ions (Fe³⁺) bound to serum transferrin. A low iron result cannot be interpreted in isolation, as it is affected by the acute phase response, low levels may be seen in infection, inflammation, and malignancy as well as in iron deficiency. Serum iron has rapidly changing concentrations in the plasma and can be impacted by meals and other diurnal variations.

Total iron binding capacity (TIBC) reflects the availability of iron binding sites on transferrin (some laboratories will measure transferrin instead of TIBC). Unlike serum iron, the TIBC/transferrin ratio does not have rapidly changing concentrations in the plasma. It is not a useful marker of early iron deficiency as values do not change until stores are depleted. TIBC/transferrin levels will increase in iron deficiency to maximise utilisation of available iron, as the body tries to compensate for low iron levels.

Percentage saturation is the percentage of transferrin bound to iron, this rises in iron overload and falls in iron deficiency but does not quantitatively reflect iron stores. A rise in serum iron due to dietary iron intake can also cause raised transferrin saturation. Percentage saturation is poorly specific, as pregnancy, oral contraceptive use, and chronic illness can result in low levels without iron deficiency. In iron deplete states, the amount of iron is reduced and therefore the transferrin saturation will be reduced. A transferrin saturation of <15% in association with an elevated TIBC is indicative of iron deficiency anaemia.

6. Absorption of oral iron (as soluble Fe²⁺) is predominantly in the duodenum and proximal jejunum. Oral ferrous sulphate, ferrous fumarate, or ferrous gluconate can be given as one tablet daily continuing for 3 months after the iron deficiency is corrected. Ferrous salts show only marginal differences in the efficiency of iron absorption; therefore, the choice of preparation is decided by the incidence of side-effects and cost. Oral iron has previously been recommended at higher doses (i.e. two to three times a day), however lower doses and more infrequent administration may be as effective and associated with less adverse effects and hence better compliance. Oral iron should be taken on an empty stomach as the absorption of iron salts is impaired by food. Taking iron with meals can reduce bioavailability by up to 75%, and absorption is reduced if taken concurrently with zinc or magnesium salts (e.g. in antacids), calcium (e.g. in milk and dairy products), tannins (e.g. in tea, coffee and cocoa) and phytates (present in cereal grains, legumes, nuts and seeds). Taking oral iron with a source of vitamin C (e.g. with a glass of orange juice) is no longer recommended as vitamin C neither enhances iron absorption nor reduces side-effects. Oral iron supplements can reduce the absorption of some drugs if taken concurrently (e.g. tetracyclines, quinolones and bisphosphonates), reducing bioavailability and clinical effect. The acidic environment of the stomach promotes iron absorption by reducing insoluble iron (Fe³⁺) to soluble iron (Fe²⁺) ions, therefore patients administering medication via jejunal tubes which bypass the stomach may require higher doses of iron or the parenteral route may be used.

7. IV iron therapy should be considered for IF patients with predicted poor oral absorption, severe IDA or those unable to tolerate oral iron. IV iron does not produce a faster Hb response than oral iron provided that the oral iron preparation is taken reliably and is absorbed adequately. It is important to consider any recent blood transfusions. One unit of transfused blood contains approximately 200-250 mg of iron.
8. Although rare, anaphylaxis can occur with IV iron administration, so close monitoring with access to resuscitation facilities is needed whenever a patient is given IV iron (and for at least 30 minutes after the infusion is complete). This reaction can occur even when a previous dose has been tolerated. Administration should be stopped immediately if any signs of an anaphylactic reaction occur.

Hypophosphatemia is another side effect thought to be caused by severe renal wasting of phosphate from the inhibition of fibroblast growth factor 23 (FGF23) degradation. It is mostly associated with ferric carboxymaltose, and occasionally with iron sucrose, and can be prolonged and refractory to phosphate replacement. Every incident of hypophosphatemia following IV iron therapy should be reported to the Medicines and Healthcare Products Regulatory Agency (MHRA) via yellow card reporting website so that the true prevalence can be ascertained. Pre-existing vitamin D deficiency, low serum calcium and/or phosphate levels may be risk factors, and these should be evaluated and corrected before administration.
9. Intramuscular iron injections are painful and involve a 2-track injection technique to avoid cutaneous siderosis. Treatment via the IM route is often unnecessary and should be avoided, utilising enteral or intravenous approaches instead.
10. Concerns regarding the potentially damaging pro-oxidant effects from elemental iron in the unwell patient make it currently ill-advised to recommend provision of iron at levels above those in the standard

reference ranges in the hyperacute situation. However, infection should not be regarded as a contraindication to IV iron if the risk/benefit assessment favours treatment of the anaemia and reducing blood transfusion requirements. IV iron should be withheld in patients with ongoing bacteraemia.

11. A full blood count (FBC) should be checked after 2-4 weeks to assess the patient's response to iron treatment. Either a restoration of a normal Hb, or an increase by at least 20 g/L in the Hb level at 4 weeks is highly suggestive of absolute iron deficiency. If there is a poor response, then the diagnosis of IDA should be reconsidered. For patients receiving HPS, ferritin can then be rechecked routinely every 3-6 months as part of the patients regular biochemical monitoring.
12. Most patients receiving HPS in the UK will be prescribed trace element preparations (such as Addaven® or Nutryelt® which contain 20 micromol [1.2 mg] and 18 micromol [1 mg] of elemental iron respectively per 10 ml ampoule). This is aligned with the ESPEN recommendation that parenteral nutrition should provide at least 1 mg/day of elemental iron. Many patients receiving HPS are given trace elements less than daily, which may be inadequate depending upon oral intake, length of functioning bowel in continuity and the underlying condition. An equivalent amount of iron may be required at periodic intervals by separate IV infusions. Additional elemental iron can be manually added to certain bespoke formulations (usually as ferric chloride) however, iron has poor compatibility with lipid formulations, and is prone to form hydrated ferric iron oxides (essentially rusts) which precipitate. It may be possible to add up to a maximum of 40 micromol (2.4 mg) of iron per litre of volume (including any amounts provided by the trace element preparation) depending on the stability data assigned to the individual formulation in order to meet the patient's requirements, or reduce the frequency of IV iron infusions.

Suggested reading

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