Iron-deficiency Anaemia

There are separate articles Childhood Anaemia and Anaemia in Pregnancy.

Iron-deficiency anaemia (IDA) occurs when the body has insufficient iron to support red blood cell production. [1]

Iron deficiency is the most common cause of anaemia worldwide. It has been identified as a modifiable risk factor for the poor development of more than 200 million children under 5 years of age in developing countries. [2]

The World Health Organization defines anaemia as: [1]

- Haemoglobin (Hb) <13 g/dL in men over 15 years old.
- Hb <12 g/dL in non-pregnant women over 15 years old.
- Hb <12 g/dL in children aged 12-14 years.

Failure to investigate IDA appropriately in primary care can cause significant delay in final diagnosis, with associated morbidity. [3]

Epidemiology

- In the developed world, 2-5% of adult men and postmenopausal women have IDA. [4]
- Iron deficiency and IDA are common in young children. [5]
- Iron deficiency is the most common cause of anaemia in pregnancy worldwide; severe anaemia can have very serious consequences for mothers and babies. [6]
- Premenopausal women have a higher incidence of IDA because of heavy menstrual blood losses and pregnancy.

Aetiology

Causes of iron deficiency may be classified as those due to:

Excessive blood loss

- Blood loss from the gastrointestinal (GI) tract is the most common cause of IDA in adult men and postmenopausal women. [4]
- Blood loss due to menorrhagia is the most common cause of iron deficiency in pre-menopausal women.
- In tropical countries, infestation of the gut may cause IDA, especially with hookworm and schistosomiasis.

Common causes of blood loss include:

- Non-steroidal anti-inflammatory drug (NSAID) use.
- Colonic carcinoma.
- Gastric carcinoma.
- Gastric or duodenal ulceration.
- Angiodysplasia.
- Heavy menstruation.

Other causes include:

- Other GI tract malignancies.
- Bleeding oesophageal varices.
- Inflammatory bowel disease.
- Haemorrhoids.
- Oesophagitis and gastro-oesophageal reflux disease.
- Postpartum haemorrhage.
- Recurrent epistaxis.
- Malignancy of the renal tract.
- After major surgery or major trauma, if replacement has been inadequate.
- After blood donation.

Dietary inadequacy

- Dietary iron deficiency is fairly uncommon.
- Meat tends to be more rich than vegetables in iron and so vegetarians are at greater risk. However, green vegetables are a good source of iron and a proper vegetarian diet should not lead to deficiency.
- Growing children and elderly people with iron-poor diets may become deficient.
Failure of iron absorption

- Not only does the diet have to contain adequate amounts of iron but the iron has to be in a form that can be absorbed.
- Iron can be absorbed in the ferrous state much more readily than in the ferric state.
- Factors affecting iron absorption:
  - Some drugs can bind to iron and prevent absorption. Tetracyclines and quinolones chelate with iron so that neither the antibiotic nor the iron is absorbed.
  - Antacids and proton pump inhibitors may also impair absorption by raising gastric pH. Antacids and proton pump inhibitors may also impair absorption by raising gastric pH. Tetracyclines and quinolones chelate with iron so that neither the antibiotic nor the iron is absorbed.
  - Phytate (found in wholegrain cereals, nuts, seeds and legumes), polyphenols (found in tea and coffee) and calcium (in dairy products) impair iron absorption. Iron absorption can be increased in a diet rich in fish, red meat and white meat. Vitamin C may enhance iron absorption. Patients can be encouraged to drink a glass of orange juice with their iron tablets. Malabsorption conditions such as coeliac disease (usually accompanied by folate deficiency). It may occur after partial or total gastrectomy, more commonly with increased number of postoperative years. Helicobacter pylori colonisation appears to impair iron uptake and increase iron loss.

Excessive requirements for iron

- Times of high demand for iron should be met by greater absorption from the diet.
- If the diet is not adequate, an intake that would otherwise be sufficient becomes inadequate - for example in:
  - Times of rapid growth in children.
  - Pregnancy, especially with twins.
  - Exfoliative skin disease.

Presentation

IDA is often an incidental finding rather than a presenting feature. Chronic, slow blood loss can lead to compensation by the body and little in the way of symptoms. If symptoms occur, they can include:

- Fatigue.
- Shortness of breath on exertion.
- Palpitations.
- Sore tongue and taste disturbance.
- Changes in the hair/hair loss.
- Pruritus.
- Headache.
- Tinnitus.
- Angina, which can occur if there is pre-existing coronary heart disease.
- Very rarely, dysphagia due to a oesophageal web with chronic iron deficiency. This is the Paterson-Brown-Kelly syndrome (or Plummer-Vinson syndrome) and there is an association with oesophageal carcinoma.

Symptoms of severe anaemia (usually not occurring until Hb is <7 g/dL) include: shortness of breath at rest, angina and ankle swelling. These symptoms may occur at higher Hb levels if there is co-existing cardiorespiratory disease.

History

Cover the following points looking for potential causes:

- Current/recent diet - poor iron intake or impaired absorption.
- Drug history - NSAIDs, selective serotonin reuptake inhibitors (SSRIs), clopidogrel, and corticosteroids could all be a potential cause.
- Any overt bleeding seen by the patient - eg, nosebleeds, rectal bleeding.
- History of recent blood donation.
- Menstrual history in women.
- History of previous GI disease or surgery.
- Travel history (eg, hookworm infestation) if there has been recent travel to the tropics.
- Family history, including inherited haematological disorders such as thalassaemia; bleeding disorders and telangiectasia; IDA, as may indicate a potential inherited disorder of iron absorption.

Examination

- Examine the abdomen for abdominal masses, organomegaly, lymphadenopathy and any other features of intra-abdominal disease.
- Rectal examination is seldom helpful unless there is rectal bleeding or tenesmus. Postpone until colonoscopy.
- If menorrhagia is thought to be the cause: perform a vaginal/bimanual examination, examine the cervix and perform a cervical smear and swabs as appropriate (see separate article Menorrhagia for further details).

Signs

- Pallor (best seen in the mucosa of the tongue and mouth, especially in people with dark skin).
- Koilonychia (spoon-shaped nails with longitudinal ridging).
Angular cheilitis (ulceration at the corners of the mouth).
Atrophic glossitis.
In marked anaemia, there may be tachycardia, a flow murmur, cardiac enlargement, ankle oedema and heart failure.

Note the spoon-shaped nail of koilonychia with the longitudinal ridges.

Other signs that may be seen include:
- Stigmata of chronic liver disease, perhaps cirrhosis.
- Multiple telangiectasias, which may be a feature of hereditary haemorrhagic telangiectasia, also known as Osler-Weber-Rendu syndrome.
- Pigmentation of the lips and oral mucosa, which may suggest Peutz-Jeghers syndrome.

Confirming the diagnosis
IDA can be diagnosed in most cases by FBC and serum ferritin level.\cite{10}

- **FBC:** shows a hypochromic microcytic anaemia (although there may be a mixed picture with co-existent B12 or folate deficiency):
  - Hypochromia means that there is a low mean corpuscular haemoglobin (MCH).
  - Microcytosis means that there is a low mean corpuscular volume (MCV).
  - Remember that a haemoglobinopathy will also cause a hypochromic microcytic anaemia.

- **Serum ferritin:** should be measured to confirm iron deficiency (except during pregnancy):
  - This correlates with total body iron stores.
  - However, ferritin levels can be raised if infection or inflammation is present, even if iron stores are low.\cite{1}
  - A cut-off ferritin level varies between 12-15 mcg/L to confirm iron deficiency.\cite{4}
  - If there is co-existing chronic inflammatory disease, the clinician should consider seeking specialist advice about other measures of iron status.

- **Blood film:** anisocytosis (variation in size between red blood cells) and poikilocytosis (abnormally shaped red blood cells) can be seen.

Differential diagnosis
Other causes of microcytic anaemia including:
- Thalassaemia.
- Sideroblastic anaemia.
- Anaemia of chronic disease.
- Lead poisoning.

Investigations\cite{4}
- Urine should be tested in all patients.
- All male and postmenopausal females should be considered for upper and/or lower GI investigations. Endoscopy or CT scan are acceptable. Endoscopy is preferred.
- All patients should be screened for coeliac disease.
If oesophagogastroduodenoscopy (OGD) is the initial investigation, lower GI endoscopy should also be performed unless advanced gastric cancer or coeliac disease is found. Even when coeliac disease has been found, consider colonoscopy if the patient is aged over 50 years or has a significant family history of colonic carcinoma.

- If there are symptoms suggesting small bowel disease or if normal iron levels cannot be restored (or maintained) by iron therapy, direct visualisation of the small bowel may be necessary.
- If the patient has recurrent IDA and normal OGD and colonoscopy, testing for (and subsequent eradication of) H. pylori is advised.
- Pre-menopausal women should have endoscopy if they are over 50 years old, or there are suggestive GI symptoms or there is a strong family history of colorectal cancer.
- Upper and lower GI investigations are recommended for patients aged over 50 years, who have had a gastrectomy.
- Only postmenopausal women and men aged over 50 years should have GI investigations of iron deficiency without anaemia.

**NB:** the appropriateness of investigating patients who are frail and/or have significant comorbidity needs to be considered on an individual basis. The severity and nature of the anaemia should be weighed against the risk of bowel preparation and whether the patient is fit enough to withstand treatment (if a colorectal cause was found).

**Who should be referred to secondary care?**[7,11]

- If someone has profound anaemia and signs of acute heart failure, they should be admitted urgently to hospital.
- Refer women with IDA and structural abnormality on pelvic ultrasound, menorrhagia unresponsive to medical management or postmenopausal bleeding to a gynaecologist.
- Refer patients to a haematologist if the type of anaemia is in doubt.
- Otherwise, refer to the gastroenterology department for urgent assessment, whether there are any GI symptoms or not.

Men of any age with unexplained IDA and an Hb level of 11 g/dL or below, should be referred within two weeks to a gastroenterologist. Women who are not menstruating, with unexplained IDA and an Hb level of 10 g/dL or below should be referred within two weeks to a gastroenterologist.

Other cases where referral to secondary care is needed:

- Someone is unable to tolerate, or is not responding to iron treatment.
- If someone who has initially responded to oral iron treatment develops anaemia again with no obvious cause.
- If a women with menorrhagia and IDA has failed to respond to treatment, she should be referred to a gynaecologist.

**Treatment**

- Treatment for the iron deficiency should be started before the results of the investigations.
- Iron salts should be given by mouth unless there are good reasons for using another route. Ferrous salts show only marginal differences between one another in efficiency of absorption of iron.[12]
- When the underlying cause is known, this should be managed appropriately.
- Iron-rich foods include dark green vegetables, meat, apricots, prunes, raisins and iron-fortified bread.[13]
- Consider referral to a dietician if diet is thought to be the cause.
- Parenteral iron is generally reserved for use when oral therapy is unsuccessful because the patient cannot tolerate oral iron or does not take it reliably, if there is continuing blood loss, or in malabsorption.[12]

**Side-effects to iron supplementation**

Common side-effects usually reduce with time and include:

- Constipation
- Black stools
- Diarrhoea
- Heartburn
- Nausea
- Abdominal/epigastric pain

**Monitoring response to treatment**

FBC should be checked 2-4 weeks after treatment has started.[7]

**If there is response to treatment**

- Check FBC again in 2-4 months to ensure Hb levels have returned to normal.
- Once Hb levels are normal, continue treatment for three months.
- Re-check FBC every three months for one year.
● Re-check again after a further year.
● If Hb or red cell indices drop below normal, give additional iron.

If there is inadequate response to treatment
● Assess compliance; is the iron supplement tolerated?
● If there are problems with compliance:
  ● Consider prescribing a laxative if constipation is experienced.
  ● Advise the patient to take iron with or after meals.
  ● Reassure the patient that black stools are normal and harmless.
  ● Reduce the frequency of the iron supplement to one or two times per day.
  ● Try a different formulation with a lower content of elemental iron - eg, ferrous gluconate.

● If oral supplements are still not tolerated, consider asking for specialist advice. If the patient is unable to tolerate oral iron or there is malabsorption, parenteral iron can be given. This is not recommended in primary care. [7]
● Transfusion is occasionally necessary and is reserved for those at risk of cardiovascular instability.
● If there is an increase of less than 2 g/dL in the Hb level after 2-4 weeks, refer for specialist assessment and advice.

Further reading & references
● NDR (Nutrition and Diet Resources) UK
  ● Investigation and Management of the Adult Patient with anaemia; Guideline Audit and Implementation Network (2015)

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4. Guidelines for the management of iron deficiency anaemia; British Society of Gastroenterology (March 2011)
7. Anaemia - iron deficiency; NICE CKS, February 2013 (UK access only)
12. British National Formulary
13. Veggie-Diets: Protecting your Health; Vegetarian and Vegan Foundation

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