Diagnosis and evaluation of iron-deficiency anaemia

In this series, we present authoritative advice on the investigation of a common clinical problem, specially commissioned for family doctors and written by members of the Royal Australasian College of Physicians.

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Iron-deficiency anaemia is a commonly encountered clinical problem usually diagnosed by the finding of microcytic, hypochromic red blood cells in association with characteristic abnormalities of iron studies (low levels of serum ferritin and serum iron, high levels of transferrin and low transferrin saturation). Diagnosis of iron-deficiency anaemia can be more difficult in patients with acute or chronic inflammatory conditions because ferritin is an acute-phase reactant.

IN SUMMARY

- **Iron-deficiency anaemia is a common condition that is usually identified by the presence of microcytic, hypochromic red cells and characteristic abnormalities of iron studies.**
- **A low serum ferritin level is the most specific serological marker of iron deficiency but it may be elevated in patients with inflammation, liver disease or malignancy.**
- **Faecal occult blood testing (FOBT) is a useful screening test for colon cancer in asymptomatic patients but is rarely useful in the setting of iron-deficiency anaemia.**
- **Initial endoscopic evaluation of patients with iron-deficiency anaemia includes gastroscopy with small bowel biopsy and colonoscopy.**
- **In one-third of patients no cause for iron-deficiency anaemia is found on gastroscopy or colonoscopy and for these patients capsule endoscopy is available on the Pharmaceutical Benefits Scheme within six months of these negative tests.**
- **Iron deficiency in the absence of anaemia is less likely to have a sinister gastrointestinal cause.**
- **Oral iron supplementation is generally well tolerated by patients, and absorption and haematological response are improved by concurrent administration of vitamin C and folate, respectively.**

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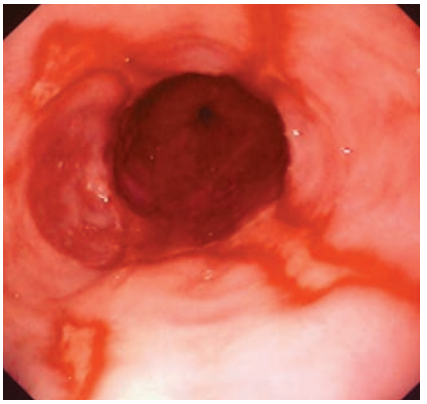

Figure 1. Endoscopic view of severe ulcerative oesophagitis in a patient with iron-deficiency anaemia.

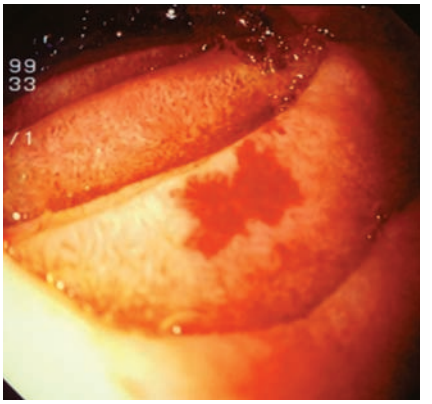

Figure 2. Endoscopic view of a small bowel angiodysplastic lesion.

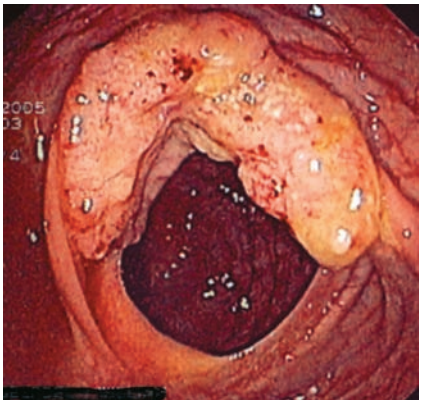

Figure 3. Endoscopic view of caecal cancer.

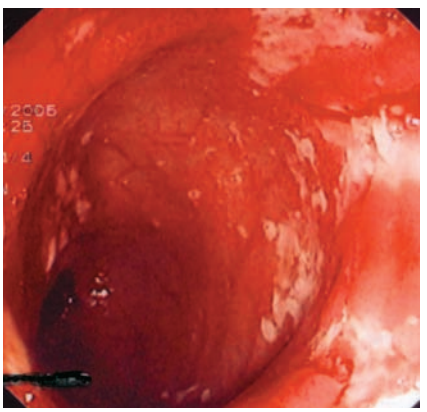

Figure 4. Endoscopic view of an inflamed terminal ileum of a patient with Crohn's disease.

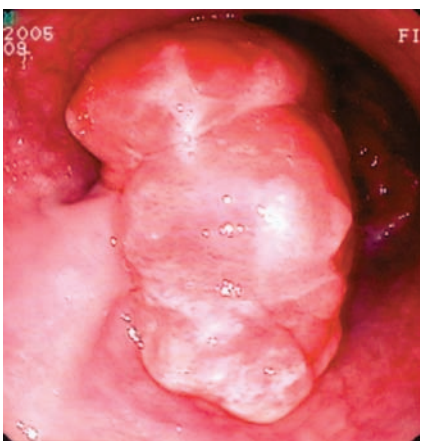

Figure 5. Endoscopic view of a large colonic polyp.

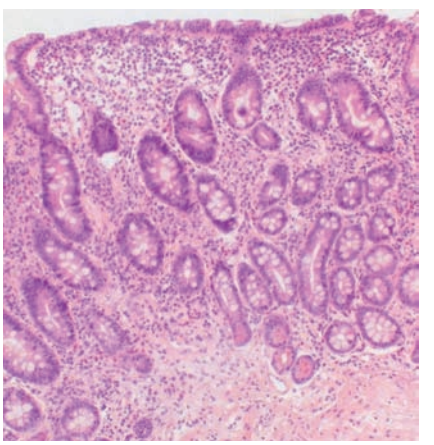

Figure 6. Small bowel histology of a patient with coeliac disease demonstrating subtotal villous atrophy.

Causes of iron deficiency include:

- blood loss (e.g. gastrointestinal [GI] bleeding, which may be overt or occult [Figures 1 to 5], menorrhagia or repeated venesection)
- reduced absorption of iron (e.g. coeliac disease [Figure 6])
- increased metabolic requirements
- inadequate dietary intake (Table 1).

GI blood loss should be considered in all patients with iron-deficiency anaemia and is the most common cause in men and postmenopausal women. Colorectal cancer is a clinically important cause of GI blood loss and in most patients with iron-deficiency anaemia the diagnostic workup should include colonoscopy to exclude this possibility.

The diagnostic evaluation of patients with iron-deficiency anaemia should be guided by a thorough history and physical examination. GI blood loss should be the presumed diagnosis in all patients unless there is a clear history of significant menorrhagia or other obvious cause such as regular blood donation. In most patients, initial evaluation of the GI tract includes gastroscopy with small bowel biopsy and colonoscopy.

Further investigations may be warranted depending on the clinical setting. Obscure GI bleeding (typically from the small bowel) after normal gastroscopy and colonoscopy results can now be investigated with capsule endoscopy. New endoscopic techniques are also expanding the therapeutic options. This review considers only anaemia due to occult bleeding. Patients with overt GI bleeding (e.g. haematemesis, melaena or haematochezia) should be evaluated differently.

Iron metabolism

Under physiological conditions, total body iron stores amount to between 3 and 4 g, with more than half (2 g) contained within circulating red blood cells. The

remainder is stored in the liver, spleen and bone marrow (0.8 to 1 g), found in proteins elsewhere in the body such as myoglobin (0.4 g) and bound to circulating transferrin (0.003 to 0.007 g).

Small amounts of iron are absorbed from dietary intake. Iron absorption occurs in the proximal small bowel and requires adequate gastric acid secretion to liberate iron from food. The typical western diet contains about 15 mg per day of elemental iron. Iron from vegetables (nonhaem iron) is poorly absorbed by the body (less than 10% of intake), whereas haem iron from meat is absorbed much more efficiently (about 30% of intake). It is important to note, however, that the iron content of fish and poultry is small compared with that in red meat. There is no physiological excretion pathway for iron, although small amounts are lost during menstruation and in the faeces due to the shedding of enteral cells.

Diagnosis of iron deficiency

The gold standard diagnostic test for iron deficiency is a bone marrow aspirate with Prussian blue staining to assess bone marrow iron stores. However, in most patients, the diagnosis of iron deficiency can be made from less invasive tests such as a blood film and iron studies. A low mean cellular haemoglobin (MCH) value (hypochromia) is more specific for iron deficiency than a low mean cellular volume (MCV; microcytosis). Additional features of iron deficiency found on a blood film include anisocytosis (variable size of red cells) and poikilocytosis (abnormally shaped red cells); however, these are not specific to iron deficiency. The differential diagnoses of hypochromic, microcytic anaemia include thalassaemia, sideroblastic anaemia and anaemia of chronic disease. Iron studies are the most useful test in differentiating these conditions (Table 2).

Thalassaemia is an inherited disorder of haemoglobin synthesis. The diagnosis may be suspected on the grounds of disproportionately reduced MCV compared with MCH or on the basis of family history or heritage. Diagnosis is confirmed by haemoglobin electrophoresis.

Sideroblastic anaemia is a hereditary or an acquired disorder of haem protein synthesis. Iron studies provide clues to the diagnosis of sideroblastic anaemia, but a definite diagnosis usually requires a bone marrow biopsy.

Anaemia of chronic disease can be difficult to distinguish from iron-deficiency anaemia on the basis of iron studies alone, and the two conditions can occur concurrently. In these circumstances, a bone marrow aspirate may be required to confirm the presence of iron deficiency.

The most commonly used iron studies are ferritin, serum iron, transferrin (also reported as total iron binding capacity) and transferrin saturation. A low ferritin level is the most specific marker of iron

Table 1. Causes of iron-deficiency anaemia

Cause	Underlying condition
Occult gastrointestinal bleeding	Colonic polyps or cancer NSAID or aspirin use Angiodysplasia (small bowel or colonic) Gastric antral vascular ectasia Gastric, oesophageal or small bowel tumours Ulcerative colitis or Crohn's disease Chronic liver disease (portal hypertensive gastropathy) Oesophagitis Hiatus hernia (large) with Cameron's ulcers Haemorrhoids Peptic ulcer disease Gastric or duodenal polyps Erosive gastritis Hookworm infestation Hereditary haemorrhagic telangiectasia
Iron malabsorption	Coeliac disease Gastric atrophy (including pernicious anaemia) Gastrectomy (complete or partial) Proximal small bowel resection or bypass Small bowel bacterial overgrowth Achlorhydria for other reasons (vagotomy)
Increased iron utilisation	Pregnancy Breastfeeding
Inadequate dietary intake	Vegetarian diet or poor intake of red meat
Extraintestinal blood loss	Menorrhagia Repeated phlebotomy or blood donation Intravascular haemolysis – including mechanical heart valves Urinary blood loss (renal cell cancer) Recurrent epistaxis Paroxysmal nocturnal haemoglobinuria

Table 2. Results of iron studies for differential diagnoses of microcytic, hypochromic anaemia

Differential diagnosis	Iron studies				
	Ferritin	Serum iron	Transferrin	Transferrin saturation	Bone marrow iron
Iron deficiency	Low	Low	High	Low	Low
Anaemia of chronic disease	Normal or high	Low	Normal or low	Normal or low	Normal or high
Thalassaemia	Normal	Normal	Normal	Normal	Normal
Sideroblastic anaemia	Normal or high	Normal or high	Normal or high	Normal or high	Normal or high (sideroblasts seen)

deficiency (specificity of 99% for ferritin levels less than 15 ng/mL and 98% for ferritin levels less than 40 ng/mL). A normal or high ferritin level does not exclude the diagnosis of iron-deficiency anaemia because levels can be elevated (but rarely by more than a factor of three) in the presence of acute or chronic inflammation, malignancy or liver disease. Concurrent measurement of C-reactive protein levels and liver function tests are useful in this regard. Generally, the serum iron level is reduced and the transferrin level is raised in patients with iron deficiency.

The transferrin saturation is calculated from these indices (100 x [serum iron/transferrin]) and is usually reduced in patients with iron-deficiency anaemia. The presence of low transferrin saturation with a low-normal serum ferritin level is also suggestive of iron deficiency. However, pregnancy and use of the oral contraceptive pill will raise serum transferrin levels and therefore lower transferrin saturation in the absence of iron deficiency. Soluble transferrin receptor is a newer test available in some laboratories to diagnose patients with iron deficiency. It is a marker of erythropoietic activity and is increased in patients with iron deficiency. Unfortunately, it has not proven to be as useful a test as initially thought and in head-to-head trials measurement of serum ferritin levels has superior sensitivity and specificity.

If doubt remains about the diagnosis of iron-deficiency anaemia after iron studies have been performed, a bone marrow biopsy is the test of choice. When the patient or clinician wish to avoid a bone marrow biopsy, an alternative diagnostic test is a therapeutic trial of iron supplementation. The diagnosis is confirmed by a resolution of the anaemia and improvement in the red cell indices. Reticulocytosis may be seen after five to seven days and the patient's haemoglobin level should increase by 200 to 400 mg/L every three to four weeks. A lack of response to iron supplementation is not helpful diagnostically and should lead to reconsideration of a bone marrow biopsy. If the diagnosis of iron-deficiency anaemia is confirmed then the usual diagnostic pathways should be followed to determine the cause.

Clinical and endoscopic evaluation

Evaluation of the patient with iron-deficiency anaemia should be guided by a thorough history and physical examination aimed at identifying potential causes of bleeding in the GI tract or other causes of the anaemia (Table 3). For medically fit men and postmenopausal women, the initial diagnostic workup should include a gastroscopy with small bowel biopsy and a colonoscopy. Gastroscopy will identify the cause of iron-deficiency anaemia in about one-third of patients, colonoscopy will identify the cause in one-third of patients and one-eighth of patients will have dual pathology. All patients should have small bowel biopsies taken to exclude the presence of coeliac disease. The strongest predictors of malignancy are age and haemoglobin levels less than 800 g/L. In patients with iron deficiency who are not anaemic, the diagnostic yield of endoscopic investigations is much lower (less than 1%).

Additional simple tests that may be helpful in establishing the cause of iron-deficiency anaemia include urinalysis for haematuria because 1% of patients with iron-deficiency anaemia have renal tract malignancy. A substantial proportion of these patients will have overt haematuria. Faecal occult blood testing (FOBT) is a useful screening test for colorectal cancer in asymptomatic, low-risk patients. However, in the setting of iron-deficiency anaemia, it plays a small part because it is not sufficiently sensitive to exclude colon cancer and a negative FOBT should not preclude endoscopic evaluation. Coeliac serology is useful in screening for coeliac disease in those patients with mild upper-gut symptoms. Anti-tissue-transglutaminase immunoglobulin IgA and IgG is the test of choice. Simultaneous measurement of serum IgA is important because IgA deficiency is not uncommon and serology may be negative in these cases. However, in patients with iron-deficiency anaemia, serology is not sufficiently sensitive to exclude the

Table 3. Clinical evaluation of iron deficiency

History

Reflux
Odynophagia
Dyspepsia
Dysphagia
Abdominal pain
Altered bowel habit (constipation or diarrhoea)
Rectal bleeding
Steatorrhoea
Menorrhagia
Haematuria
Blood donation
Epistaxis
Aspirin or NSAID use
Dietary history
Previous gastric surgery
Weight loss
Family history of malignancy

Physical examination

Features of iron deficiency

Glossitis
Angular stomatitis
Koilonychia

Physical findings suggesting cause

Abdominal mass or organomegaly
Mass on digital rectal examination
Lymphadenopathy
Oral or facial telangiectasia
Signs of chronic liver disease
Abdominal scar
Signs of malnutrition
Mouth ulcers

diagnosis and therefore is of questionable use in the evaluation of these patients.

Premenopausal women are a difficult group to diagnose because iron deficiency is commonly due to menstrual loss or the increased demands of pregnancy and breastfeeding. Furthermore, malignant tumours are relatively uncommon and dietary iron intake may be lower in this population. Those with GI symptoms or risk factors for malignancy (such as a family history) should proceed to endoscopic evaluation. For patients under the age of 50 years who have no symptoms and no risk factors, a therapeutic trial of iron supplements may be appropriate after addressing other potential causes of iron deficiency such as menorrhagia and dietary intake. If the iron deficiency recurs or does not respond to iron therapy then endoscopic evaluation should be undertaken. There may be some role for FOBT and coeliac serology in the evaluation of iron-deficiency anaemia in this group.

Obscure gastrointestinal bleeding

For patients with no cause found for their iron deficiency after initial endoscopic evaluation, a number of approaches are reasonable but the clinician should be guided by the clinical context and specialist advice. For patients with mild iron-deficiency anaemia who are otherwise considered unlikely to have sinister GI pathology, a therapeutic trial of iron supplements may be reasonable with close follow up. Alternatively, evaluation for small bowel causes of iron-deficiency anaemia may be undertaken, including small bowel series, CT enterography, enteroscopy or capsule endoscopy (Figure 7).

Small bowel series have been largely replaced by CT enterography, which has the advantage of being able to detect both intestinal and extraintestinal GI causes of iron-deficiency anaemia (e.g. renal tract malignancies). However, in common with small bowel series, intestinal mucosal vascular abnormalities such as angiodysplasia (the most common cause of obscure, small bowel bleeding) can not be diagnosed with CT enterography. Push enteroscopy allows detection of vascular lesions and also permits therapy but is invasive and rarely able to access the entire small bowel mucosa. Newer techniques such as balloon enteroscopy are most useful as therapeutic rather than diagnostic procedures. These techniques remain relatively invasive, are time consuming and their availability is geographically limited.

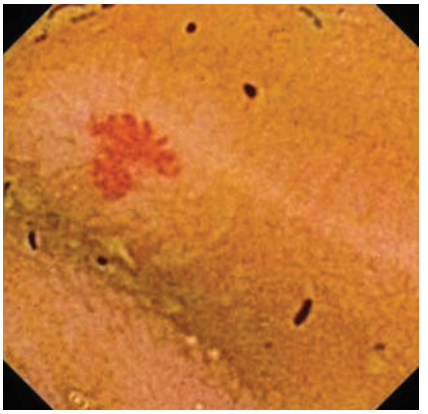

Figure 7. Small bowel vascular lesion as seen by capsule endoscopy.

Since 2005 capsule endoscopy has been reimbursed under the Pharmaceutical Benefits Scheme (PBS) for the investigation of patients with iron-deficiency anaemia. To qualify for the rebate for capsule endoscopy, the patient must have anaemia from 'recurrent or persistent bleeding' or have 'active bleeding'. The patient must also have had both a gastroscopy and colonoscopy performed within the preceding six months. Capsule endoscopy is relatively noninvasive, well tolerated and has a higher yield for small bowel causes of iron-deficiency anaemia than other investigations (radiological or endoscopic). The procedure will also identify lesions missed at gastroscopy in a significant proportion of patients. The disadvantage of capsule endoscopy is that it does not permit biopsy or therapy for identified lesions.

Correction of iron deficiency

After identification and treatment of the causative factor of iron-deficiency anaemia,

correction of the iron deficiency should be undertaken. Although improved dietary iron intake is advisable, it is rarely sufficient to replenish significantly depleted iron stores within a reasonable time frame.

Oral iron supplements (usually ferrous sulfate preparations) are simple to use, inexpensive and generally well tolerated. An adequate dose of oral iron is more than 150 mg of elemental iron per day (two to three tablets of a ferrous sulfate preparation; each tablet usually contains between 55 and 105 mg of elemental iron).

The concurrent use of vitamin C supplements will improve absorption, and folate supplementation can improve the haematological response to oral iron. Preparations of iron combined with vitamin C or folate are available. Oral iron supplements should not be taken with food because food will reduce their absorption. Dose-dependent constipation or nausea will be experienced by 10 to 20% of patients taking orally administered iron and they should be warned about this possibility. In these circumstances, the dose may be reduced to improve tolerability.

Supplementation should continue until the anaemia is resolved (usually three to six months) and a further six months of therapy should be undertaken to ensure adequate replenishment of body stores. Failure to respond to iron supplementation may be due to noncompliance, malabsorption, incorrect diagnosis, intercurrent disease (such as renal failure) or ongoing GI loss. All patients should be monitored for recurrence of anaemia or iron deficiency.

Parenterally administered iron is more invasive, more expensive and has a risk of significant side effects. However, it can provide a much larger quantity of iron more quickly and may be appropriate for some patients (such as those with cancer, inflammatory bowel disease or renal failure, particularly those on dialysis). It may also be used in those who do not tolerate oral iron supplementation. Intramuscular delivery is slow, unreliable and often painful. Furthermore, the quantity of elemental iron provided is not significantly greater than that absorbed from an adequate dose of oral iron. Intravenously administered iron (iron infusion) is available as a hospital day procedure. There are reports of serious adverse reactions including death (although rare and more common with the older, higher molecular weight preparations no longer routinely used) and administration of intravenous iron should not be undertaken without consideration of these risks.

Conclusion

Iron-deficiency anaemia is common and usually diagnosed by characteristic abnormalities of iron studies. Its diagnosis should initiate careful evaluation for the cause as well as the correction of the iron deficiency. GI bleeding is the most common cause of iron-deficiency anaemia in men and postmenopausal women and all medically fit patients should be evaluated for a GI cause. Young women with an obvious reason for the anaemia such as menorrhagia or regular blood donation and no GI symptoms or abnormal physical findings represent a special case in which a therapeutic trial of iron supplementation with close observation and follow up may be appropriate. MT

References

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