

Guidelines for the management of iron deficiency anaemia

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A F Goddard, MW James, A S McIntyre and BB Scott on behalf of the BSG

EXECUTIVE SUMMARY

Background

Colonic cancer, gastric cancer and coeliac disease are the most important gastrointestinal causes of iron deficiency anaemia.

Definitions

- The lower limit of the normal range should be used to define anaemia (B)
- Iron deficiency should be confirmed by a low serum ferritin, red cell microcytosis or hypochromia in the absence of chronic disease or haemoglobinopathies (A).
- Any level of iron deficiency anaemia should be investigated

Investigations

- Rectal examination and urine testing should be performed
- All patients should be screened for coeliac disease (B).
- Upper and lower GI investigations should be considered in all male patients unless there is a history of significant overt non-GI blood loss (A).
- Upper and lower GI investigation should be considered for female patients who are post-menopausal, aged over 50 years or older, or have a strong family history of colorectal cancer
- Colonoscopy has advantages over barium enema for investigation of the lower GI tract in IDA, but either is acceptable (B).
- Further direct visualisation of the small bowel is probably not necessary unless the IDA is transfusion dependent (B).
- Faecal occult blood testing is of no benefit in the investigation of IDA (B).
- Only post-menopausal women and men aged over 50 years should have GI investigation of iron deficiency without anaemia (C).

Management

- All patients should have iron supplementation both to correct anaemia and replenish body stores (B).
- Parenteral iron can be used when oral preparations are not tolerated (C).

SCOPE

These guidelines are primarily intended for gastroenterologists and GI surgeons but are applicable for other doctors seeing patients with IDA. The investigation of overt blood loss is not considered in these guidelines.

INTRODUCTION

Iron deficiency anaemia (IDA) has a prevalence of 2-5% among adult men and post-menopausal women in the developed world¹² and is a common cause of referral to gastroenterologists (4-13% of referrals)3. While menstrual blood loss is the commonest cause of IDA in pre-menopausal women, blood loss from the gastrointestinal (GI) tract is the commonest cause in adult men and post-menopausal women⁴⁻⁹. Asymptomatic colonic and gastric carcinoma may present with IDA and seeking these conditions is a priority in patients with IDA. Malabsorption (most frequently from coeliac disease in the UK), poor dietary intake, blood donation, gastrectomy and NSAID use are not uncommon causes of IDA and there are many other possible causes (Table 1). IDA is often multifactorial. The management of IDA is often suboptimal with most patients being incompletely investigated if not at all¹⁰ 11. Dual pathology, i.e. the presence of significant GI bleeding in upper and lower GI tracts, is uncommon but does occur in 1-10% of patients⁴⁻⁹.

TABLE 1. Causes of iron deficiency anaemia with prevalence as percentage of total4-9

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Occult GI Blood Loss	
Common	
 Aspirin/NSAID use 	10-15%
Colonic carcinoma	5–10%
 Gastric carcinoma 	5%
 Benign gastric ulceration 	5%
 Angiodysplasia 	5%
Uncommon	
 Oesophagitis 	2–4%
 Oesophageal carcinoma 	1–2%
 Gastric antral vascular ectasia 	1–2%
 Small bowel tumours 	1–2%
 Ampullary carcinoma 	<1%
Ancylomasta duodenale	<1%
Malabsorption	
Common	
 Coeliac disease 	4–6%
 Gastrectomy 	<5%
H. pylori colonisation	<5%
Uncommon	
• Gut resection	<1%
 Bacterial overgrowth 	<1%
Non-GI Fblood loss	
Common	
Menstruation	20-30%
Blood donation	5%
Uncommon	
Haematuria	1%
• Epistaxis	<1%
*	

DEFINITIONS

Anaemia

The WHO defines anaemia as a haemoglobin below 13 g/dL in men over 15 years, below 12 g/dL in non-pregnant women over 15 years, and below 11 g/dL in pregnant women¹². The diagnositic criteria for anaemia in IDA vary between published studies⁴⁻⁹. The normal range for haemoglobin also varies between different populations in the UK. Therefore, it is reasonable to use the lower limit of the normal range for the laboratory performing the test to define anaemia (B).

There is little consensus as to the level of anaemia that requires investigation. The Department of Health referral guidelines for suspected lower GI cancer suggest that only patients with Hb less than 11 g/dl in men or less than 10 g/dl in postmenopausal women be referred, despite there being no supporting evidence¹³. A cut-off value of 8 g/dL has been shown to be the most discriminatory for detecting patients with and without cancer (regardless of gender), but this value lacks sensitivity⁹. It is recommended that any level of anaemia should be investigated in the presence of iron deficiency (B).

Iron deficiency

Modern automated cell counters provide measurements of the changes in red cells which accompany iron deficiency: reduced mean cell haemoglobin (MCH) - hypochromia and increased percentage of hypochromic red cells, and reduced mean cell volume (MCV) – microcytosis¹⁴. MCH is probably the more reliable because it is less influenced by the counting machine used and by storage. Both microcytosis and hypochromia are sensitive indicators of iron deficiency in the absence of chronic disease or co-existent B₁₂ or folate deficiency¹⁵. An increased red cell distribution width (RDW) will often indicate co-existent B₁₂ or folate deficiency. Microcytosis and hypochromia are also present in many haemoglobinopathies (such as thalassaemia, when the MCV is often out of proportion to the level of anaemia compared with iron deficiency and, on review of previous results, has never been normal), in sideroblastic anaemia and in some cases of anaemia of chronic disease. Haemoglobin electrophoresis is especially recommended when microcytosis is longstanding and in patients of appropriate ethnic background to prevent unnecessary GI investigation (C).

The serum markers of iron deficiency are low ferritin, low iron, raised total iron binding capacity, raised red cell protoporhyrin and increased transferrin binding receptors (sTfR). Serum ferritin is the most powerful test for iron deficiency (A). The cut-off level of ferritin which is diagnostic varies between 12–15 $\mu mg/L$ (12,16,17). This value only holds for patients without co-existent disease. In such settings, a cut-off value of <50 $\mu mg/L$ is still consistent with iron deficiency i. The sTfR level is said to be a good marker of iron deficiency in healthy subjects (18) but its utility in the clinical setting remains to be proven. Several studies show that the sTfR/log10 serum ferritin ratio provides superior discrimination to either test on its own, particularly in chronic disease. 19 .

Further tests to confirm iron deficiency are occasionally necessary. Estimation of iron concentration in bone marrow by the histochemical method¹⁴ may distinguish between 'true' iron deficiency and other chronic disorders in which there is impaired release of iron from reticuloendothelial cells, but is subjective. A therapeutic trial of oral iron for three weeks is less invasive and may aid diagnosis, but depends on compliance. A trial of parenteral iron may be more reliable, and a measurable change in MCH should occur within 7 days when there is iron deficiency anaemia.

Functional Iron Deficiency

"Functional iron deficiency" occurs where there is an inadequate iron supply to the bone marrow in the presence of storage iron in reticuloendothelial cells. Perhaps the most important clinical setting for this is in patients with renal failure who will require parenteral iron therapy to respond to administered erythropoietin to correct anaemia.

None of the currently available tests have more than fair utility for deciding which patients will benefit from parenteral iron in this setting²⁰. Low reticulocyte haemoglobin content provides an early indication of functional iron deficiency²¹, whilst a reduced percentage of hypochromic erythrocytes is a good predictor of response²².

INVESTIGATIONS

History

Borderline iron deficient diets are common and a dietary history should be taken to identify poor iron intake. The use of aspirin and non-aspirin-NSAIDs should be noted and these drugs stopped where the clinical indication is weak or other choices are available. Family history of IDA (which may indicate inherited disorders of iron absorption²³), haematological disorders (e.g. thalassaemia), telangiectasia and bleeding disorders should be sought. A history of blood donation should be obtained.

The presence of one or more of these factors in the history should not, however, usually deter further investigation.

Examination

Examination is usually non-contributory but may reveal a relevant abdominal mass or cutaneous signs of rare causes of GI blood loss (e.g. Peutz-Jeghers syndrome and hereditary haemorrhagic telangiectasia). Rectal examination should be performed (though this may be postponed until colonoscopy).

Urine testing for blood is recommended in all patients with IDA (B) as approximately 1% of patients with IDA will have renal tract malignancy. Anaemia occurs in approximately one third of patients with renal cell carcinoma²⁴ due to haematuria and haemosiderin deposition in the tumour. Further renal tract evaluation with ultrasound is recommended where suspicion of renal tract malignancy is strong followed by IVU and/or CT scan as necessary.

Upper and lower GI evaluation

Upper and lower GI investigations should be considered in all post-menopausal female and all male patients where IDA has been confirmed unless there is a history of significant overt non-GI blood loss. In the absence of suggestive symptoms (which are unreliable) the order of investigations is determined by local availability. The appropriateness of investigating patients with severe co-morbidity or other reasons (in some circumstances advanced age), especially if the result would not influence management, should be carefully discussed with patients and carers when possible.

All patients should be screened for coeliac disease (B). Ideally coeliac serology (either anti-endomysial antibody – EMA or tissue transglutaminase antibody – tTG) should be taken at presentation. If coeliac serology is negative small bowel biopsies then need not be taken at oesophago-gastro-duodenoscopy (OGD) unless there are other features which make coeliac disease more likely (B). If coeliac serology is positive, coeliac disease is likely and should be confirmed by small bowel biopsy. Further GI investigations (including colonoscopy) are not necessary in this setting. However, the lifetime risk of GI malignancy in patients with coeliac disease is slightly increased²⁵, and if IDA develops in

a patient with treated coeliac disease upper and lower GI investigation is recommended.

If OGD is done as the initial GI investigation, only the presence of gastric cancer or coeliac disease should deter lower GI investigation (B). In particular, the presence of oesophagitis, erosions and peptic ulcer disease should not be accepted as the cause of IDA until lower GI investigations have been done. Small bowel biopsies should be taken at OGD if coeliac serology is positive or not done.

Colonoscopy (possibly at the same session as OGD) has the advantage that it will demonstrate angiodysplasia and allow biopsy of any lesion. However, double contrast barium enema is a sufficient alternative^{26 27}, with or without sigmoidoscopy^{26 28} especially if the facilities for colonoscopy are limited or the success rate of complete colonoscopy is poor within a particular unit.

Further evaluation

Further direct visualisation of the small bowel is probably not necessary unless the IDA is transfusion dependent (B)^{3 7}. Follow-up studies have shown this approach to be safe^{26 29} provided dietary deficiency is corrected, NSAIDs have been stopped and the haemoglobin concentration is monitored. However, if IDA is transfusion dependent, enteroscopy may be helpful to detect and treat angiodysplasia^{30 31}. Video capsule endoscopy (VCE) can also be used in this setting and has a diagnostic yield of 40–55%^{32 33}. Many lesions detected by both enteroscopy and VCE are within the reach of a gastroscope, and repeat OGD should be considered prior to these procedures. Small bowel radiology is rarely of use unless the history is suggestive of Crohn's disease⁵.

Helicobacter pylori colonisation may impair iron uptake and increase iron loss thus leading to iron deficiency and IDA^{34–36}. Eradication of *H. pylori* appears to reverse anaemia in anecdotal reports and small studies³⁷. *H. pylori* should be sought if OGD and colonoscopy are normal and eradicated if present (C).

Mesenteric angiography is of limited use but may be of value in transfusion dependent IDA for demonstrating vascular malformations. Similarly, diagnostic laparotomy with on-table endoscopy may be considered in cases which have defied diagnosis by other investigations.

Other investigations, including routine assessments of the liver and renal function, and clotting studies are of no diagnostic value unless the history is suggestive of systemic disease³. Faecal occult blood testing is of no benefit in the investigation of IDA (B), being insensitive and non-specific⁴ ³⁸ ³⁹.

MANAGEMENT

Aim of treatment

The aim of treatment should be to restore haemoglobin levels and red cell indices to normal, and replenish iron stores. If this cannot be achieved, consideration should be given to further evaluation.

Iron therapy

Treatment of an underlying cause should prevent further iron loss but all patients should have iron supplementation both to correct anaemia and replenish body stores (B)²⁻⁴⁰. This is achieved most simply and cheaply with ferrous sulphate 200 mg twice daily. Lower doses may be as effective and better tolerated⁴¹⁻⁴² and could be considered in patients not tolerating traditional doses. Other iron compounds (e.g. ferrous fumarate, ferrous gluconate) or formulations (iron suspensions) may also be tolerated better then ferrous sulphate. Ascorbic acid (250–500 mg twice daily with the iron preparation) may enhance iron absorption⁴³. We recommend that oral iron is continued until three months after the iron deficiency has been corrected so that stores are replenished.

Parenteral iron may be used when there is intolerance or non-compliance with oral preparations. Intravenous iron sucrose, when given according to the manufacturers' instructions, is reasonably well tolerated (35% of patients have mild side effects) with a low incidence of serious adverse reactions (0.03–0.04%)⁴⁴⁴⁵. Bolus intravenous dosing of iron sucrose (200mg iron) over 10 minutes is licensed and more convenient than a two-hour infusion. Intravenous iron dextran can replenish iron and haemoglobin levels in a single infusion. but serious reactions can occur (0.6–0.7%) and there have been fatalities associated with infusion (31 reported between 1976–1996)⁴⁴⁴⁵. However, it can be given via the intramuscular route when venous access is problematic.

Blood transfusions should be reserved for patients with, or at risk of, cardiovascular instability due to their degree of anaemia (C), particularly if they are due to have endoscopic investigations before a response from iron treatment is expected (46). Transfusions should aim to restore haemoglobin to a safe level, but not necessarily normal values. Iron treatment should follow transfusion to replenish stores.

Follow-up

Once normal, the haemoglobin concentration and red cell indices should be monitored at intervals. We suggest three monthly for one year then again after a further year. Additional oral iron should be given if the haemoglobin or red cell indices fall below normal (ferritin levels can be reserved for cases where there is doubt). Further investigation is only necessary if the haemoglobin and red cell indices cannot be maintained in this way. It is reassuring to know that iron deficiency does not return in most patients in whom a cause for IDA is not found after OGD, small bowel biopsy and barium enema²⁶.

Summary flow chart

A management chart is shown in Figure 1.

SPECIAL CONSIDERATIONS

Investigation of pre-menopausal women

IDA occurs in 5–12% of otherwise healthy pre-menopausal women⁴⁷ and is usually due to menstrual loss, increased demands in pregnancy and breast-feeding, or dietary deficiency49. The yield of GI investigation in these 'patients' has been investigated in several studies⁵⁰⁻⁵⁸. Malignant tumours have been found in 0-6.5% of patients, but the two studies with highest detection rates^{52 56} have been criticised as non-representative⁵⁸. It therefore seems likely that, although malignant tumours may occur in asymptomatic pre-menopausal women, they are extremely uncommon. Coeliac disease is present in up to 4% of premenopausal women in these studies. All pre-menopausal women with IDA should be screened for coeliac disease (B). Age is the strongest predictor of pathology in patients with IDA9, and thus GI investigation as outlined above is recommended for asymptomatic pre-menopausal women with IDA aged 50 years or older (B).

OGD should be considered for any pre-menopausal women with IDA and upper GI symptoms according to the Department of Health referral guidelines for suspected upper GI cancer¹³.

Colonic investigation in pre-menopausal women aged less than 50 years should be reserved for those with colonic symptoms, a strong family history (one affected first degree relative <45 years old, or two affected first degree relatives⁵⁹), or persistent IDA following iron supplementation and correction of potential causes of losses (for example menorrhagia, blood donation, and poor diet).

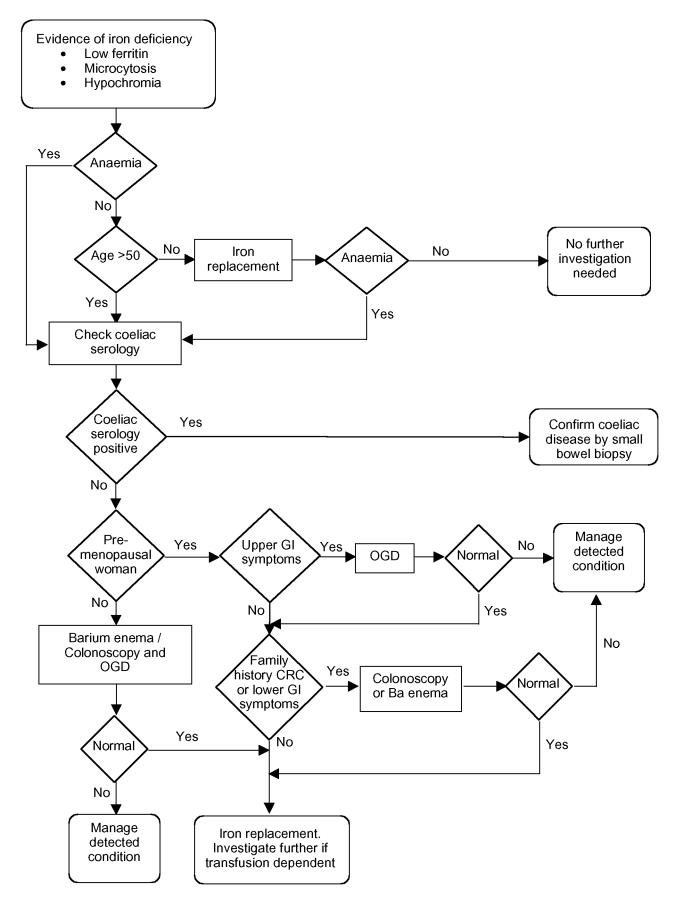


FIGURE 1. Management of iron deficiency in adults

Although it is convenient to use the term pre-menopausal, it is menstruation which influences the investigative pathway. It is probably wise to fully investigate those pre-menopausal women who have IDA but no menstruation (e.g. after hysterectomy).

Young men

Although the incidence of important GI pathology in young men is low, there are no data on the yield of investigation in those with IDA. In the absence of such data we recommend that young men should be investigated the same as older men (C).

Post-gastrectomy

IDA is very common both in patients with partial or total gastrectomy60, probably due to poor chelation and absorption of iron as a result of loss of ascorbic acid and hydrochloric acid, and loss of free iron in exfoliated cells. However, these patients also have a two- to three fold increased risk of gastric cancer after 20 years, and probably an increased risk of colon cancer. Investigation of IDA in post-gastrectomy patients aged over 50 years of age is therefore recommended (C).

Iron deficiency without anaemia

Iron deficiency without anaemia (as proven by a low serum ferritin - hypoferritinaemia) is three times as common as IDA55, but there is little consensus on whether these patients should be investigated. The largest study shows very low prevalence of GI malignancy in patients with iron deficiency alone (0.9% of postmenopausal women and men, and 0% of pre-menopausal women)55. Higher rates have been reported only in more selected groups⁶¹ 62. The evidence therefore suggests that only postmenopausal women and men aged over 50 years should have GI investigation of hypoferritinaemia (C).

SUGGESTED TARGETS FOR AUDIT

We suggest that:

- 90% of patients with IDA should be screened for coeliac
- 90% of patients (other than menstruating women) with IDA and no obvious cause should have both an upper GI endoscopy and either colonoscopy or barium enema (unless carcinoma or coeliac disease is found is found).
- 90% of patients receive appropriate iron replacement.
- 90% of those not responding to treatment should be considered for further investigation.
- In 100% of patients being investigated for iron deficiency anaemia reasonable evidence for iron deficiency anaemia should be documented in the notes by an appropriate Hb, MCH and MCV or ferritin, or there should be an explanation why iron deficiency is suspected in patients not showing typical blood test results.

QUALITY OF EVIDENCE

The quality of evidence for recommendations based in theses guidelines is as follows:

- Grade A Based on meta-analysis or large randomised controlled studies
- Based on good evidence from small or non-Grade B randomised studies
- Grade C Based on specialist opinion

DATE FOR REVIEW

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These guidelines have been prepared by the British Society of Gastroenterology. They represent a consensus of best practice based on the available evidence at the time of preparation. They may not apply in all situations and should be interpreted in the light of specific clinical situations and resource availability.