Guidelines for the management of iron deficiency anaemia

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ABSTRACT

Background

- Iron deficiency anaemia (IDA) occurs in 2–5% of adult men and postmenopausal women in the developed world and is a common cause of referral to gastroenterologists. Gastrointestinal (GI) blood loss from colonic cancer or gastric cancer, and malabsorption in coeliac disease are the most important causes that need to be sought.

Defining iron deficiency anaemia

- The lower limit of the normal range for the laboratory performing the test should be used to define anaemia (B).
- Any level of anaemia should be investigated in the presence of iron deficiency (B).
- The lower the haemoglobin the more likely there is to be serious underlying pathology and the more urgent is the need for investigation (B).
- Red cell indices provide a sensitive indication of iron deficiency in the absence of chronic disease or haemoglobinopathy (A).
- Haemoglobin electrophoresis is recommended when microcytosis and hypochromia are present in patients of appropriate ethnic background to prevent unnecessary GI investigation (C).
- Serum ferritin is the most powerful test for iron deficiency (A).

Investigations

- Upper and lower GI investigations should be considered in all postmenopausal female and all male patients where IDA has been confirmed unless there is a history of significant overt non-GI blood loss (A).
- All patients should be screened for coeliac disease (B).
- If oesophagogastroduodenoscopy (OGD) is performed as the initial GI investigation, only the presence of advanced gastric cancer or coeliac disease should deter lower GI investigation (B).
- In patients aged >50 or with marked anaemia or a significant family history of colorectal carcinoma, lower GI investigation should still be considered even if coeliac disease is found (B).
- Colonoscopy has advantages over CT colography for investigation of the lower GI tract in IDA, but either is acceptable (B). Either is preferable to barium enema, which is useful if they are not available.
- Further direct visualisation of the small bowel is not necessary unless there are symptoms suggestive of small bowel disease, or if the haemoglobin cannot be restored or maintained with iron therapy (B).
- In patients with recurrent IDA and normal OGD and colonoscopy results, *Helicobacter pylori* should be eradicated if present. (C).
- Faecal occult blood testing is of no benefit in the investigation of IDA (B).
- All premenopausal women with IDA should be screened for coeliac disease, but other upper and lower GI investigation should be reserved for those aged 50 years or older, those with symptoms suggesting gastrointestinal disease, and those with a strong family history of colorectal cancer (B).
- Upper and lower GI investigation of IDA in post-gastrectomy patients is recommended in those over 50 years of age (B).
- In patients with iron deficiency without anaemia, endoscopic investigation rarely detects malignancy. Such investigation should be considered in patients aged >50 after discussing the risk and potential benefit with them (C).
- Only postmenopausal women and men aged >50 years should have GI investigation of iron deficiency without anaemia (C).
- Rectal examination is seldom contributory, and, in the absence of symptoms such as rectal bleeding and tenesmus, may be postponed until colonoscopy.
- Urine testing for blood is important in the examination of patients with IDA (B).

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).
- Blood transfusions should be reserved for patients with or at risk of cardiovascular instability due to the degree of their anaemia (C).

SCOPE

These guidelines are primarily intended for Western gastroenterologists and gastrointestinal (GI) surgeons, but are applicable for other doctors seeing patients with iron deficiency anaemia (IDA). They are not designed to cover patients with overt blood loss or those who present with GI symptoms. GI symptoms or patients at particular risk of GI disease should be investigated on their own merits.

INTRODUCTION

IDA occurs in 2–5% of adult men and postmenopausal women in the developed world[1 2] and is a common cause of referral to gastroenterologists (4–13% of referrals).[3] While menstrual blood loss is the most common cause of IDA in premenopausal women, blood loss from the GI tract is the most common cause in adult men and postmenopausal women.[4–9] Asymptomatic colonic and gastric carcinoma may present with IDA, and seeking these conditions is a priority in patients with IDA. Malabsorption (most commonly from coeliac disease in the UK), poor dietary intake, blood donation, gastrectomy and use of non-steroidal

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anti-inflammatory drugs (NSAIDs) are common causes of IDA, and there are many other possible causes (table 1). IDA is often multifactorial. Its management is often suboptimal, with most patients being incompletely investigated or not investigated at all.[10 11] Dual pathology—that is, the presence of a significant cause of bleeding in both upper and lower GI tracts—may occur in 1–10% of patients or more[4–9] and should be increasingly considered the older the patient.

DEFINING IDA

Anaemia

The World Health Organization defines anaemia as a haemoglobin (Hb) concentration below 13 g/dl in men over 15 years of age, below 12 g/dl in non-pregnant women over 15 years of age, and below 11 g/dl in pregnant women.[1] The diagnostic criteria for anaemia in IDA vary between published studies.[4–9] The normal range for Hb 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 NHS National Institute for Health and Clinical Excellence referral guidelines for suspected lower GI cancer suggest that only patients with Hb concentration <11 g/dl in men or <10 g/dl in non-menstruating women be referred.[12] It has been suggested that these cut-off values miss patients with colorectal cancer, especially men.[13] It is therefore recommended that any level of anaemia should be investigated in the presence of iron deficiency. Furthermore, it is recommended[13] that men with Hb concentration <12 g/dl and postmenopausal women with Hb concentration <10 g/dl should be investigated more urgently, since lower levels of Hb suggest more serious disease (A).

Table 1 Pathological contributors to iron deficiency anaemia in the UK with prevalence as percentage of total[4–9]

Contributor	Prevalence
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%
Cameron ulcer in large hiatus hernia	<1%
Ampullary carcinoma	<1%
Ancylomasta duodenale	<1%
Malabsorption	
Common	
Coeliac disease	4–6%
Gastrectomy	<5%
Helicobacter pylori colonisation	<5%
Uncommon	
Gut resection	<1%
Bacterial overgrowth	<1%
Non-GI blood loss	
Common	
Menstruation	20–30%
Blood donation	5%
Uncommon	
Haematuria	1%
Epistaxis	<1%

GI, gastrointestinal; NSAID, non-steroidal anti-inflammatory drug.

Iron deficiency

Modern automated cell counters provide measurements of the changes in red cells that accompany iron deficiency: reduced mean cell Hb (MCH)—hypochromia—and increased percentage of hypochromic red cells and reduced mean cell volume (MCV)—microcytosis.[14] The 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 coexistent vitamin B_{12} or folate deficiency.[15] An increased red cell distribution width will often indicate coexistent vitamin B_{12} 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), in sideroblastic anaemia and in some cases of anaemia of chronic disease. Hb electrophoresis is recommended when microcytosis is present in patients of appropriate ethnic background to prevent unnecessary GI investigation (C).

The serum markers of iron deficiency include low ferritin, low transferrin saturation, low iron, raised total iron-binding capacity, raised red cell zinc protoporphyrin, and increased serum transferrin receptor (sTfR). Serum ferritin is the most powerful test for iron deficiency in the absence of inflammation (A). The cut-off concentration of ferritin that is diagnostic varies between 12 and 15 μg/l.[16 17] This only holds for patients without coexistent inflammatory disease. Where there is inflammatory disease, a concentration of 50 μg/l or even more may still be consistent with iron deficiency.[1] The sTfR concentration 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 have shown that the $sTfR/\log_{10}$ 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 method[14] may distinguish between 'true' iron deficiency and other chronic disorders in which there is impaired release of iron from cells of the monocyte–macrophage system (previously known as reticuloendothelial cells), but is subjective and seldom performed. A therapeutic trial of oral iron for 3 weeks is less invasive and may aid diagnosis, but depends on compliance. A trial of parenteral iron may be more reliable, and a significant change in MCH should occur within 7 days when there is IDA.

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 cells of the monocyte–macrophage system. Perhaps the most important clinical setting for this is in patients with renal failure who require parenteral iron therapy to respond to administered erythropoietin to correct anaemia. Functional iron deficiency also occurs in many chronic inflammatory diseases (eg, rheumatoid arthritis and inflammatory bowel disease)—the anaemia of chronic disease.

None of the currently available tests have more than fair utility for deciding which patients will benefit from parenteral

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iron in this setting.[20] Low reticulocyte Hb content provides an early indication of functional iron deficiency,[21] while a reducing percentage of hypochromic erythrocytes is a good predictor of response.[22]

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 absorption[23]), haematological disorders (eg, thalassaemia), telangiectasia and bleeding disorders should be sought. A history of blood donation or any other source of blood loss should be obtained. The presence of one or more of these factors in the history should not, however, usually deter further investigation. A significant family history of colorectal carcinoma should be sought—that is, one affected first-degree relative <50 years old or two affected first-degree relatives. A previous history of IDA may alter the order or appropriateness of tests, especially if longstanding.

Examination

Examination usually contributes little but may reveal a relevant abdominal mass or cutaneous signs of rare causes of GI blood loss (eg, Peutz–Jeghers syndrome and hereditary haemorrhagic telangiectasia). Rectal examination is seldom contributory in patients with IDA, and, in the absence of symptoms such as rectal bleeding and tenesmus, may be postponed until colonoscopy unless there is likely to be significant delay. Urine testing for blood is recommended in all patients with IDA (B), as ~1% of patients with IDA will have renal tract malignancy.[9] Anaemia occurs in approximately one-third of patients with renal cell carcinoma,[24] and this is due to haematuria and haemosiderin deposition in the tumour. Further renal tract evaluation with ultrasound is recommended if haematuria is found, followed by intravenous urography and/or CT scan as necessary.

Upper and lower GI evaluation

Upper and lower GI investigations should be considered in all postmenopausal 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, although all patients should be screened for coeliac disease with serology (B)—see below. If oesophagogastroduodenoscopy (OGD) is performed as the initial GI investigation, only the presence of gastric cancer or coeliac disease, as explained below, 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 carried out. Small-bowel biopsy samples should be taken at OGD if coeliac serology was positive or not performed. Colonoscopy has the following advantages over radiology: it allows biopsy of lesions, treatment of adenomas, and identification of superficial pathology such as angiodysplasia and NSAID damage. Performing gastroscopy and colonoscopy at the same session speeds investigation and saves time for both the hospital and the patient, because only one attendance for endoscopy is required. Radiographic imaging is a sufficient alternative where colonoscopy is contraindicated. The sensitivity of CT colography for lesions >10 mm in size is over 90%.[25] Barium enema is less reliable, but is still useful[26] if colonoscopy or CT colography are not readily available.

Screening for and further investigation of coeliac disease

Ideally coeliac serology—tissue transglutaminase (tTG) antibody [27] or endomysial antibody if tTG antibody testing is not available—should be undertaken at presentation, but if this has not been carried out or if the result is not available, duodenal biopsy specimens should be taken. If coeliac serology is negative, small-bowel biopsies need not be performed at OGD unless there are other features, such as diarrhoea, which make coeliac disease more likely (B). The pretest probability of coeliac disease in those with IDA alone is ~5%. The negative likelihood ratio for the tTG antibody test using human recombinant tTG is 0.06.[27] Thus, if the tTG antibody test is negative, the post-test probability of coeliac disease is 0.3%, which is less than in the general population. This means that duodenal biopsy samples will need to be taken from ~330 tTG antibody-negative patients to detect one extra patient with coeliac disease at an estimated additional cost of £35 000. If coeliac serology is positive, coeliac disease is likely and should be confirmed by small-bowel biopsy. Although concurrent testing for IgA deficiency, which is found in 2% of patients with coeliac disease, has been recommended, we do not consider it necessary to test for it routinely, because it only results in the post-test probability of coeliac disease with a negative tTG antibody test changing slightly from 0.3% to 0.2%, which is not clinically significant. However, it is advised[28] if low absorbance readings are shown in the IgA tTG antibody assay.

Further GI investigations are not usually necessary if coeliac disease is diagnosed. However, the lifetime risk of GI malignancy in patients with coeliac disease is slightly increased,[29] particularly within 1 year of diagnosis, so investigation with colonoscopy should be considered if additional risk is present—for example, if age is >50 years or if there is a significant family history of colorectal carcinoma. If IDA develops in a patient with treated coeliac disease, upper and lower GI investigation is recommended in those aged >50 in the absence of another obvious cause. In the rare case of normal small-bowel histology with positive serology, we recommend that investigation should proceed as if coeliac serology was negative.

Further evaluation

Further imaging of the small bowel is probably not necessary unless there is an inadequate response to iron therapy, especially if transfusion dependent (B).[3 7] Follow-up studies have shown this approach to be reasonably safe[26 30 31] provided that dietary deficiency is corrected, NSAIDs have been stopped, and the Hb concentration is monitored.

In those with an inadequate response, video capsule endoscopy or enteroscopy may be helpful to detect angiodysplasia, Crohn's disease and small-bowel neoplasia.[32 33] Video capsule endoscopy has a diagnostic yield of 40–55%[32–34] in this setting. However, it seldom results in a beneficial subsequent intervention.[35] Many lesions detected by both enteroscopy and video capsule endoscopy are within the reach of a gastroscope, and repeat OGD should be considered before these procedures. Bleeding lesions identified by video capsule endoscopy may be amenable to treatment by push or double-balloon enteroscopy. However, the benefits of these procedures after a normal video capsule endoscopy in the context of IDA are unproven.

Small-bowel imaging (MRI enteroclysis, CT enterography or barium studies) should also be considered in patients with symptoms suggestive of small-bowel disease, transfusion-dependent IDA, and rapid recurrence of anaemia after normalisation of Hb concentrations. However, many small intestinal lesions that cause asymptomatic anaemia are mucosal and flat or nearly so and most small intestinal imaging modalities apart

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from video capsule endoscopy are only efficient at identifying mass lesions. CT has the additional advantage of being able to identify extraintestinal pathology such as renal tumours and lymphomas.

Helicobacter pylori colonisation may impair iron uptake and increase iron loss, potentially leading to iron deficiency and IDA.[36–39] Eradication of *H pylori* appears to reverse anaemia in anecdotal reports and small studies.[40] *H pylori* should be sought by non-invasive testing, if IDA persists or recurs after a normal OGD and colonoscopy, and eradicated if present (C). *H pylori* urease (CLO) testing of biopsy specimens taken at the initial gastroscopy is an alternative approach.

Autoimmune gastritis has been identified as a potential cause of IDA in up to a quarter of cases,[41 42] but, although of interest, its diagnosis is currently of little practical value.

Giardia lamblia has occasionally been found during the investigation of IDA. If there is associated diarrhoea, then small-bowel biopsy samples will be taken anyway and may detect this. Where giardiasis is suspected, stool should be sent for ELISA, even if histology of duodenal biopsy samples is negative.

Radiological imaging of the mesenteric vessels is of limited use but may be of value in transfusion-dependent IDA for demonstrating vascular malformations or other occult lesions. Similarly, diagnostic laparotomy with on-table enteroscopy is rarely required in cases that have defied diagnosis by other investigations. There is no evidence to recommend labelled red cell imaging or Meckel's scans in patients with IDA.

Other investigations, including routine assessments of the liver and renal function, and clotting studies are of no diagnostic value unless the history suggests systemic disease.[3] Faecal occult blood testing is of no benefit in the investigation of IDA (B), being insensitive and non-specific.[4 43 44]

MANAGEMENT

Aim of treatment

After attending to any discovered underlying cause, the aim of treatment should be to restore Hb concentrations 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).[45] This is achieved most simply and cheaply with ferrous sulphate 200 mg twice daily. Lower doses may be as effective and better tolerated[46 47] and should be considered in patients not tolerating traditional doses. Other iron compounds (eg, ferrous fumarate, ferrous gluconate) or formulations (iron suspensions) may also be tolerated better than ferrous sulphate. Oral iron should be continued for 3 months after the iron deficiency has been corrected so that stores are replenished.

Ascorbic acid (250–500 mg twice daily with the iron preparation) may enhance iron absorption,[48] but there are no data for its effectiveness in the treatment of IDA.

For those intolerant or not responding to oral iron, there are three parenteral preparations available, two of which can only be administered intravenously (iron sucrose (Venofer) and ferric carboxymaltose (Ferinject)), and one that can be given either intravenously or by deep gluteal intramuscular injection (iron (III) hydroxide dextran (Cosmofer)), although this can be painful and requires several injections. A comparison of intravenous iron compounds is shown in table 2. The principal advantage of ferric carboxymaltose, a recent addition to intravenous therapy, is the abbreviated duration of infusion, without the need for a test dose—15 min compared with 6 h with Cosmofer (consisting of a 15 min test dose, 45 min observation, 4 h infusion, then 1 h observation). Although drug costs are higher, length of stay in a day-case or primary-care facility is reduced.

Table 2 Comparison of the intravenous iron preparations

Intravenous iron preparation	Maximum single dose	Duration of infusion	Cost/g of iron†
Iron dextran* (Cosmofer)	20 mg/kg	6 h	£79.70
Iron sucrose (Venofer)	200 mg	10 min	£70.80
	500 mg	4 h	
Ferric carboxymaltose (Ferinject)	1000 mg	15 min	£217.50
	But ≤15 mg/kg		

*Can also be given intramuscularly.
†Costs according to British National Formulary.

Intravenous iron sucrose is reasonably well tolerated (35% of patients have mild side effects including abdominal pain, nausea, headache and diarrhoea), with a low incidence of serious adverse reactions (0.03–0.04%).[48 49] Bolus intravenous dosing of iron sucrose (200 mg iron) over 10 min is licensed and more convenient than a 2 h infusion. Intravenous iron dextran can replenish iron and Hb concentrations 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 and 1996).[49 50] The incidence of side effects with ferric carboxymaltose are similar to other intravenous compounds (22–29%),[51 52] but no anaphylaxis has been reported to date. The cautions and contraindications found in the manufacturers' instructions and in the British National Formulary should be noted. Anaphylaxis may occur, and resuscitation facilities should be available for all these agents when given intravenously. Although the initial rise in Hb is more rapid with parenteral iron,[53] the rise in Hb at 12 weeks is similar to that observed during oral iron therapy.[4 51 52]

Blood transfusions should be reserved for patients with symptomatic anaemia despite iron therapy or at risk of cardiovascular instability because of their degree of anaemia (C), particularly if they are due to have endoscopic investigations before a response from iron treatment is expected.[54] Transfusions should aim to restore Hb to a safe level, but not necessarily normal values. Iron treatment should follow transfusion to replenish stores.

Follow-up

Once normal, the Hb concentration and red cell indices should be monitored at intervals. We suggest 3 monthly for 1 year, then after a further year, and again if symptoms of anaemia develop after that. Further oral iron should be given if the Hb or red cell indices fall below normal (ferritin concentrations can be reserved for cases where there is doubt). Further investigation is only necessary if the Hb and red cell indices cannot be maintained in this way. It is reassuring that iron deficiency does not recur in most patients in whom a cause is not found after upper GI endoscopy, testing for coeliac disease, and large-bowel investigation.[26 31]

Summary flow charts for investigation and treatment

An abbreviated investigation flow chart is shown in figure 1 and an abbreviated treatment flow chart in figure 2. They both should be used in conjunction with the text.

SPECIAL CONSIDERATIONS

Investigation of premenopausal women

IDA occurs in 5–12% of otherwise healthy premenopausal women[55 56] and is usually due to menstrual loss, increased

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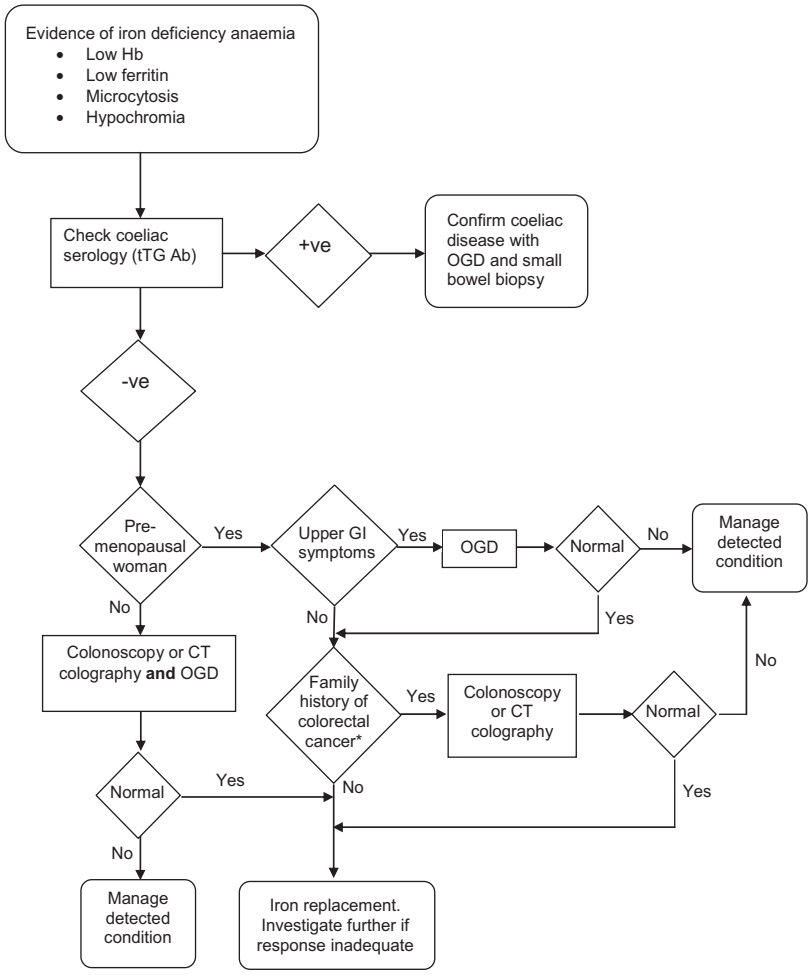


Figure 1 An abbreviated flow chart of the investigation of iron deficiency anaemia. GI, gastrointestinal; Hb, haemoglobin; OGD, oesophagogastroduodenoscopy; tTG Ab, tissue transglutaminase antibody. *See text for details of significant family history.

demands in pregnancy and breast feeding, or dietary deficiency.[57] The yield of GI investigation in these 'patients' has been investigated in several studies.[58–66] Malignant tumours have been found in 0–6.5% of patients, but the two studies[64–66] with highest detection rates have been criticised as non-representative. It therefore seems likely that, although malignant tumours may occur in asymptomatic premenopausal women, they are extremely uncommon. Coeliac disease is present in up to 4% of premenopausal women in these studies. All premenopausal women with IDA should be screened for coeliac disease (B). Age is the strongest predictor of pathology in patients with IDA,[9] and thus GI investigation as outlined above is recommended for asymptomatic premenopausal women with IDA aged 50 years or older (B).

OGD should be considered for any premenopausal women with IDA and upper GI symptoms according to the Department of Health referral guidelines for suspected upper GI cancer.[12]

Colonic investigation in premenopausal women aged <50 years should be reserved for those with colonic symptoms, a strong family history (two affected first-degree relatives or just one first-degree relative affected before the age of 50 years[67]), or persistent IDA after iron supplementation and correction of potential causes of losses (eg, menorrhagia, blood donation and poor diet).

Although it is convenient to use the term premenopausal, it is menstruation that influences the investigative pathway. Thus those premenopausal women who have IDA but no menstruation (eg, after hysterectomy) should be fully investigated.

Patients with significant comorbidity

The appropriateness of investigating patients with frailty and/or severe comorbidity needs to be considered on a case-by-case basis. Factors to be taken into account include the severity and recurrent nature of the anaemia, the risk of bowel preparation before lower GI investigation, and the potential fitness of the patient to withstand treatment in the event that a colorectal cause was identified. The least invasive test should be used where deemed appropriate. There are no data in the literature about the detection rate of cancer in patients with IDA being investigated with unprepared CT or minimally prepared CT compared with standard CT colography or colonoscopy. Provisional data from the national bowel cancer screening programme show a pick up rate of 6.9% for minimal or unprepared CT (101 patients) compared with 11% for colonoscopy (>33 000 patients). Thus, although unprepared CT may miss occasional cancers, we continue to recommend this for very frail patients in whom bowel preparation may be risky. An older patient with weight loss may benefit from an initial CT scan of the abdomen, pelvis and thorax, and, if malignancy is found, endoscopy may not be necessary.

Patients awaiting surgery

Prompt and effective iron replacement is needed before urgent surgery, and intravenous iron is a likely cost-effective solution that may obviate the need for blood transfusion.

Young men

Although the incidence of important GI pathology in young men is low, there are no data on the yield of investigation in

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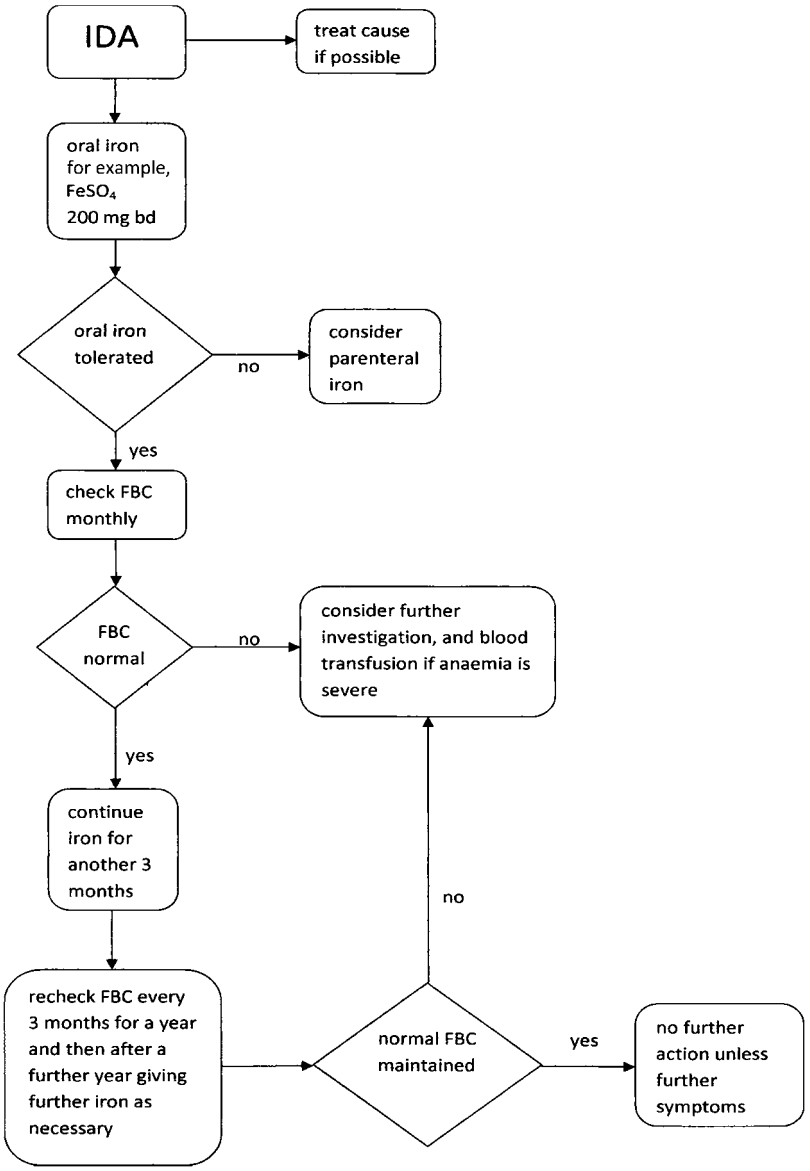


Figure 2 An abbreviated flow chart of the treatment of iron deficiency anaemia (IDA). bd, twice a day; FBC, full blood count.

those with IDA. In the absence of such data, we recommend that young men should be investigated in the same manner as older men (C). Where there is an obvious cause of blood loss (eg, blood donation), it is reasonable to avoid investigations unless anaemia recurs despite correction of the cause of blood loss.

Pregnant women

Mild IDA is common in pregnancy, and iron replacement should be encouraged as soon as the diagnosis is made. A careful history and examination should be made, specifically seeking a family history of gastrointestinal neoplasia or coeliac disease. Coeliac serology should be carried out. If it is positive, endoscopy and duodenal biopsy can be performed, as there is no evidence this is unsafe in pregnancy. If there is concern about lower GI pathology, further investigation should be considered, although in some patients this may be delayed until after delivery. Performing unsedated flexible sigmoidoscopy in pregnancy is considered quite safe.[68] However, there are insufficient data on the safety of performing colonoscopy in pregnancy, and, because of its potential to cause serious adverse events, it should be reserved for very strong indications.[68] MR colography is believed to be safe for mother and fetus and should be preferred to radiological imaging. The National Radiological Protection Board considers it prudent to avoid MRI in the first trimester.

Post-gastrectomy

IDA is very common in patients with partial or total gastrectomy,[69] probably because of 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 >50 years of age is therefore recommended (C). Bariatric surgery can lead to iron deficiency, but iron supplementation is usually recommended after surgery to prevent the problem.

Use of warfarin and aspirin

No significant difference in the prevalence of GI cancer was found in patients taking aspirin or warfarin, either alone or in combination, compared with patients not taking these drugs.[9] IDA should therefore not be attributed to these drugs until GI investigations have been completed.

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Use of proton pump inhibitor

There are no data to indicate that proton pump inhibitors cause IDA in humans. Patients taking these drugs should not be considered less likely to have malignancy.

Iron deficiency without anaemia

Iron deficiency without anaemia (confirmed by low serum ferritin-hypoferritinaemia) is three times as common as IDA,[63] but there is no consensus on whether these patients should be investigated, and further research is needed. 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 premenopausal women).[63] Higher rates have been reported only in more selected groups.[70 71] In the absence of firm evidence, we tentatively recommend coeliac serology in all these patients but that other investigation be reserved for those with higher-risk profiles (eg, age >50 years) after discussion of the risks and potential benefits of upper and lower GI investigation (C). All others should be treated empirically with oral iron replacement for 3 months and investigated if iron deficiency recurs within the next 12 months (C).

SUGGESTED QUALITY STANDARDS

We suggest that:

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

QUALITY OF EVIDENCE

The system for grading quality of evidence and strength of recommendations in these guidelines is based on the Scottish Intercollegiate Guidelines Network methodology as follows:

Level	Type of evidence	Grade of recommendation
IA	Meta-analysis of randomised controlled trials or inception cohort studies	A
IB	At least one randomised controlled trial or well-designed cohort studies with good follow-up	A
IIA	At least one well-designed controlled study without randomisation or a meta-analysis of case–control studies	B
IIB	At least one study with quasi-experimental design or case–control study	B
III	At least one non-experimental study (such as a descriptive study)	C
IV	Expert committee reports or reports by recognised authorities	C

Authors' note It is with deep sadness that we record Dr Alistair McIntyre's sudden and premature death after completing these revised guidelines. His wide knowledge and experience and his common sense contributed greatly to the success of the previous guidelines. His co-authors had great pleasure in working with him since 1999.

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