Guidelines for the management of iron deficiency anaemia

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Summary
Iron deficiency anaemia in men and post-menopausal women is most commonly caused by gastrointestinal blood loss or malabsorption. Examination of both the upper and lower gastrointestinal tract is therefore an important part of the investigation of patients with such anaemia. In the absence of overt blood loss or any obvious cause, all patients should have upper gastrointestinal endoscopy, including small bowel biopsy, and colonoscopy or barium enema to exclude gastrointestinal malignancy. Further gastrointestinal investigation is only warranted in transfusion dependent anaemia or where there is visible blood loss. Treatment of an underlying cause will cure the anaemia but even when no cause is detected the long term outlook is good.

1.0 Introduction

Iron deficiency anaemia (IDA) occurs in 2–5% of adult men and post-menopausal women in the developed world[1 2] and is a common cause of referral to a gastroenterology clinic (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 women.[4–8] Asymptomatic colonic and gastric carcinoma may present with IDA and exclusion of these conditions is of prime concern. Malabsorption (most frequently from coeliac disease), poor dietary intake, previous gastrectomy, and NSAID use are not unusual but there are many other possible causes (table 1). The management of IDA is often suboptimal with most patients being incompletely investigated if at all.[9]

These guidelines are primarily for gastroenterologists and GI surgeons but would be applicable to other doctors seeing patients with IDA.

The investigation of overt blood loss is not considered in these guidelines.

2.0 Definitions

2.1 ANAEMIA

The diagnostic criteria for anaemia in IDA vary (Hb <10–11.5 g/dl for women and <12.5–13.8 g/dl for men) between studies. The lower limit of the normal range of haemoglobin concentration for the laboratory performing the test should therefore probably be used to define anaemia*. It is not known at what level of haemoglobin investigations should be initiated. However, there is no a priori reason why mild anaemia should be less indicative of important disease than severe anaemia.

Table 1 Gastrointestinal (GI) diseases presenting with iron deficiency

Occult GI blood loss
Common
NSAID use
Colonic cancer/polyp
Gastric cancer
Angiodysplasia
Crohn's disease
Ulcerative colitis
Uncommon
Oesophagitis†
Peptic ulcer†
Oesophageal cancer
Water melon stomach
Intestinal telangiectasia
Lymphoma, leiomyoma and other small bowel tumours
Duodenal polyp (Brunner's gland adenoma)
Carcinoma of the ampulla of Vater
Meckel's diverticulum
Hookworm
Malabsorption
Coeliac disease
Gastrectomy (partial and total) and gastric atrophy
Gut resection or bypass
Bacterial overgrowth
Whipple's disease
Lymphangiectasia

†Although common causes of acute bleeding they are uncommon causes of occult bleeding.

2.2 IRON DEFICIENCY (ID)

Microcytosis (mean corpuscular volume (MCV) lower than the normal range) is characteristic of ID but it may also occur in much less common conditions such as thalassaemia (when the red cell count is usually elevated). Haemoglobinopathies frequently cause microcytosis in certain ethnic groups but this should not be presumed to be the cause unless confirmed by laboratory testing. Microcytosis may be absent in combined deficiency (e.g. with folate deficiency) which may be recognised by a raised red cell distribution width (RDW). The anaemia of chronic disease due to the inability to use iron may also present with microcytosis.

Serum ferritin concentration is the most powerful test for ID*** .[10] A serum ferritin concentration of <12 μg/dl is diagnostic of ID**.[11] However, serum ferritin may be raised above 12–15 μg/dl in patients with ID and concurrent chronic inflammation, malignancy, or hepatic disease, although if the concentration is >100 μg/dl, ID is almost certainly not present.

A further test is usually only required in patients when doubt still remains as to the presence of iron deficiency**[11 12] and advice from a haematologist should be sought. Red cell protoporphyrin concentration and

Abbreviations used in this paper: ID, iron deficiency; IDA, iron deficiency anaemia; RDW, red cell distribution width; GI, gastrointestinal; MCV, mean corpuscular volume.

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- Serum ferritin concentration is the most powerful test for iron deficiency***.

transferrin saturation of <30% may help the diagnosis but a therapeutic response to three weeks of oral iron or a bone marrow aspiration are the only ways of confirming true deficiency***.[10] New tests which involve measuring the serum transferrin binding receptor/ferritin ratio show promise in distinguishing between anaemia of chronic disease and iron deficiency but are not yet widely available.

The need for investigation of patients with iron deficiency but no anaemia has not been assessed in clinical studies.

3.0 Investigations

3.1 HISTORY

A careful dietary history is important to identify iron deficient diets. However, since borderline deficient diets are common in patients, a positive dietary history should not be presumed as the cause of anaemia and a full GI investigation is still required. The presence of upper and lower GI symptoms should be documented although these rarely correlate with investigation findings. The use of aspirin and analgesics, particularly NSAIDs, should be noted and stopped whenever possible. The use of these drugs and anticoagulants should not usually deter investigation. Family history of haematological disorders (for example thalassaemia and sideroblastic anaemia), telangiectasia, and bleeding disorders should be sought.

3.2 EXAMINATION

Careful examination, although seldom contributory, may reveal a relevant abdominal mass or cutaneous signs of gastrointestinal blood loss (for example Peutz-Jeghers and Osler-Weber-Rendu syndromes).

3.3 GASTROINTESTINAL EVALUATION

GI investigations should be considered in all patients in whom IDA has been confirmed unless there is a history of significant non-GI blood loss. In the absence of suggestive symptoms the order of investigations will be determined by local availability. It is usually convenient to do upper GI endoscopy first although in the elderly investigation of the colon is likely to be more productive. Upper GI endoscopy can be expected to reveal a cause in between 30 and 50% of patients.[4–8] Small bowel biopsies should be taken during this endoscopy as 2–3% of patients presenting with IDA have coeliac disease**.[3 4 6] If the patient is unable to have upper GI endoscopy, a barium meal should be performed in addition to blood antiendomysial antibody.

- Small bowel biopsies should be taken during endoscopy as 2–3% of patients presenting with iron deficiency anaemia have coeliac disease**.

Unless the upper GI endoscopy reveals carcinoma or coeliac disease, all patients should then undergo examination of the lower GI tract***[1 3–8] as dual pathology (lesions in both the colon and upper GI tracts) occurs in around 10–15% of patients. In particular, oesophagitis, erosions, aphthous ulceration, and peptic ulcer should not at this stage be accepted as the cause of the iron deficiency. Colonoscopy (possibly at the same session as the upper GI endoscopy—'bidirectional endoscopy') has the advantage that it will demonstrate angiodysplasia and allow biopsy of any lesion. However, double contrast barium enema is a sufficient alternative,[13 14] with or without sigmoidoscopy*,[13] especially if the facilities for colonoscopy are limited or the success rate of complete colonoscopy is poor within a particular unit. Omission of sigmoidoscopy appears safe if digital rectal examination is negative in the absence of a changed bowel habit or rectal bleeding.[13]

3.4 FURTHER EVALUATION

Further direct visualisation of the small bowel is probably not necessary unless the IDA is transfusion dependent or there has been visible blood loss**.[3 7] Follow-up studies have shown this approach to be safe[13 15] provided dietary deficiency is corrected and/or NSAIDs stopped and the haemoglobin concentration monitored. However, if IDA is transfusion dependent, enteroscopy may be helpful to detect and treat small bowel angiodysplasia**.[16 17] Small bowel radiology is rarely of use unless the history is suggestive of Crohn's disease**.[5 18] Mesenteric angiography is of limited use but may be valuable in transfusion dependent IDA for demonstrating vascular malformations. Similarly, diagnostic laparotomy with on-table endoscopy may be considered in cases which have defied other investigation but is unlikely to be resorted to unless there is transfusion dependent anaemia*.[2] Meckel's diverticulum usually presents with visible blood loss (melaena) but may rarely present with IDA and should be considered in young adults. Diagnostic laparotomy is the most sensitive test for Meckel's diverticulum while pertechnicate scans have very poor sensitivity**.[19]

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 disease**.[3] Faecal occult blood testing is of no benefit in the investigation of IDA, being insensitive and non-specific**.[4 20] Very occasionally, urinary tract tumours may present with IDA and therefore the presence of haematuria should be excluded.

4.0 Management

4.1 AIM OF TREATMENT

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

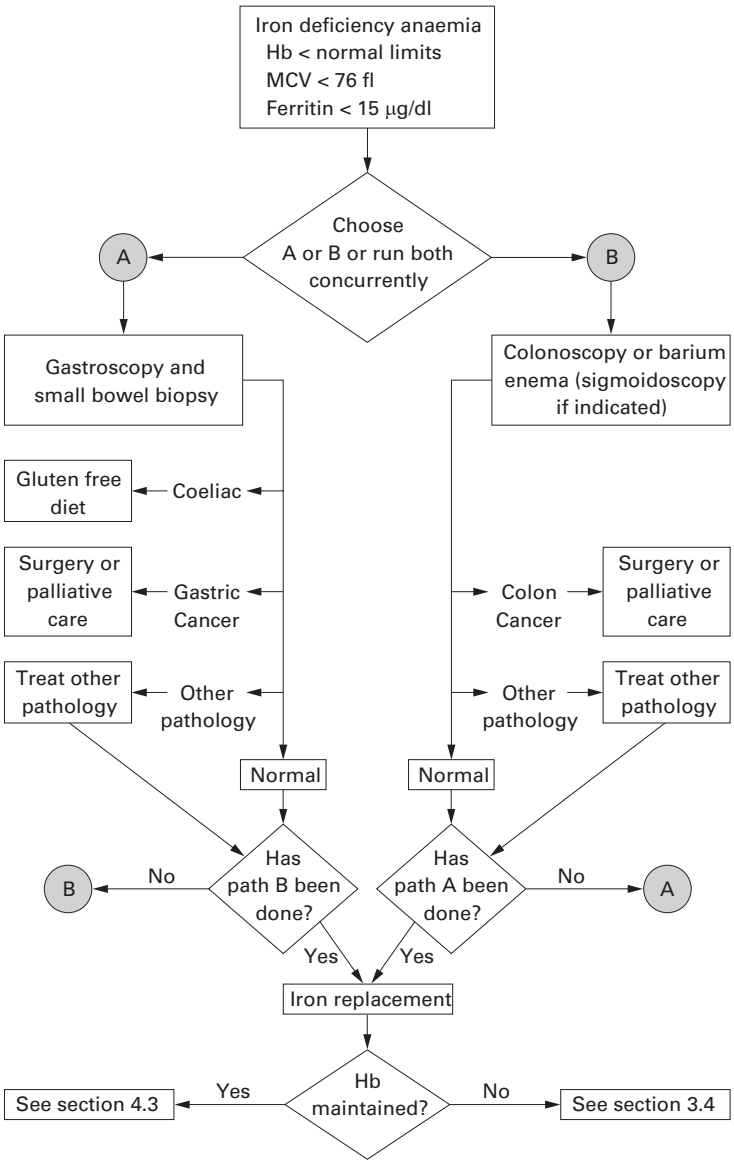

Figure 1 Flow chart for the management of iron deficiency anaemia in men and non-menstruating women (for other patient groups see text).

4.2 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★★.[2 21] This is achieved most simply and cheaply with ferrous sulphate 200 mg three times daily although ferrous gluconate and ferrous fumarate are as effective.[21] A liquid preparation may be tolerated when tablets are not. Ascorbic acid enhances iron absorption★★[22] and should be considered when response is poor. Parenteral iron should only be used when there is intolerance to at least two oral preparations or non-compliance. Parenteral iron treatment is painful (when given intramuscularly), expensive, and may cause anaphylactic reactions. The rise in haemoglobin is no quicker than with oral preparations. The haemoglobin concentration should rise by 2 g/dl after 3–4 weeks. Failure to do so is usually due to poor compliance, misdiagnosis, continued blood loss, or malabsorption. Iron supplementation should be continued for three months after correction of anaemia to replenish iron stores★.[21]

- All patients should receive iron supplementation to correct anaemia and replenish body stores★★.

4.3 FOLLOW UP

Once normal, the haemoglobin concentration and red cell indices should be monitored at intervals. We suggest three monthly for one year and then after a further year. Additional oral iron should be given if the haemoglobin or MCV falls below normal (a ferritin estimation should also be done in doubtful cases). Further investigation is only necessary if the haemoglobin and MCV 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 upper GI endoscopy, small bowel biopsy and barium enema.[13]

4.4 SUMMARY FLOW CHART

A management flow chart is shown in fig 1.

5.0 Special considerations

5.1 CO-MORBIDITY

The appropriateness of investigating patients with severe co-morbidity or other reason (in some circumstances advanced age) especially if the result would not influence management, should be carefully considered and discussed with patients and carers when possible.

5.2 PRE-MENOPAUSAL WOMEN

Menstruating women present a large healthy population in which IDA is common, occurring in 5–10%.[23] Menstrual loss, especially menorrhagia, pregnancy, and breast feeding are usually responsible.[24] History is unreliable in quantifying menstrual loss,[25] although pictorial blood loss assessment charts have been shown to have a sensitivity and specificity of around 80% for detecting menorrhagia.[26] There are little data on the yield of GI investigation in menstruating women with IDA[27 28] but significant GI pathology has been detected in these studies.

- Iron deficiency anaemia occurs in 5–10% of menstruating women.

Because of the increasing incidence of important pathology with age, we recommend that those more than 45 years are investigated according to the above guidelines. In the absence of data in those less than 45 years, we recommend that only patients with upper GI symptoms have endoscopy and small bowel biopsy. The remainder should have antiendomysial antibody determinations (and IgA measurement to exclude IgA deficiency which makes the test unreliable) to exclude coeliac disease. Colonic investigation in patients less than 45 years should only be done if there are

colonic symptoms, a strong family history of colorectal carcinoma (for example two first degree relatives or one first degree relative <45 years), or persistent IDA following iron supplementation and correction of potential causes of losses (for example menorrhagia, blood donation, poor diet).

5.3 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 investigation of young men should occur according to the guidelines.

5.4 POST-GASTRECTOMY

IDA is to be expected after gastrectomy, both partial and total,[29] due to poor chelation and absorption of iron as a result of the loss of ascorbic acid and hydrochloric acid, and loss of free iron in exfoliated cells. It would seem reasonable, therefore, only to investigate those whose IDA persists on iron supplementation or who present with IDA many years after partial gastrectomy.

6.0 Suggested targets for audit

We suggest that:

- 90% of patients (other than menstruating women) with iron deficiency anaemia and no obvious cause should have both an upper GI endoscopy with small bowel biopsy and either colonoscopy or barium enema (unless a firm cause is found with the first investigation).
- Resolution of anaemia should be achieved by six months in 80% of patients.
- 90% of those not responding to treatment should have been considered for further investigation.

7.0 Suggested topics for further research

- The need to investigate iron deficiency without anaemia.
- The importance of stratifying for risk of significant disease according to haemoglobin level.
- The long term prognosis of colonic neoplasms discovered by investigating iron deficiency anaemia compared with those found in other ways.
- The role of investigation in young men and menstruating women.
- The value of CT colonography in the investigation of IDA.

8.0 Strength of recommendations made in these guidelines

The strength of evidence for recommendations given in these guidelines is indicated by *, **, or *** in the text as follows:

***Based on meta-analysis or large randomised trials.

**Based on good evidence from trials, but less convincing (e.g. smaller numbers).

*Based on specialist opinion.

9.0 Formulation of guidelines

These guidelines were drawn up by the following process:

(1) Medline search using the term "iron deficiency anaemia".
(2) Review of abstracts of all references.
(3) Review of all papers felt to be relevant to guidelines.
(4) Review of references not cited by Medline felt to be relevant to guidelines.
(5) Drafts of guidelines formulated by authors.
(6) Initial guidelines reviewed by BSG Clinical Services and Standards Committee.
(7) Guidelines amended by authors.
(8) Steps (6) and (7) repeated twice.
(9) Guidelines accepted by BSG Clinical Services and Standards Committee.
(10) Guidelines reviewed by BSG council.
(11) Guidelines amended by authors.
(12) Guidelines accepted by council and submitted for publication.

10.0 Date for review

April 2004.

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