

Iron deficiency anaemia – a gastroenterologist's perspective

Iron deficiency is one of the commonest causes of anaemia in adults.

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Peter Barrow has a special interest in inflammatory bowel disease (IBD), coeliac disease, oesophageal motility and endoscopic ultrasound. In 2005 he worked at the Free University of Amsterdam, the Netherlands – a referral centre for small-bowel disorders (including Crohn's and coeliac disease).

In premenopausal women menstrual blood loss is the commonest, but not the only, cause of iron deficiency. In men and women over 50, gastrointestinal (GIT) blood loss becomes more important and may be the only marker of significant GIT pathology, such as colonic or gastric cancer. There are many other GIT causes for iron deficiency anaemia, including poor dietary intake, previous gastrectomy, NSAID use and malabsorption (most likely due to coeliac disease in patients of European origin, even in South Africa).

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As colon and gastric cancer are two of the most common causes of cancer death world wide, an iron deficiency anaemia, however mild, should never be ignored or treated empirically without further GIT investigation – especially in men and women over 50. It is therefore important to diagnose and investigate iron deficiency according to evidence-based guidelines.¹ It is a common reason for referral to gastroenterologists, accounting for at least 9% of referrals to the Johannesburg Hospital medical gastroenterology clinic.²

Definition

Up to 39% of patients referred to the Johannesburg Hospital gastroenterology clinic for presumed iron deficiency anaemia were incorrectly labelled after further investigation.² This is similar to other studies globally and highlights the importance of correct diagnosis of this common disorder as described in other articles in this issue of *CME*.

Because the diagnostic criteria for anaemia vary (haemoglobin <10 - 11.5 g/dl for women and 12.5 - 13.8 g/dl for men), the lower limit of normal range of the haemoglobin concentration for the

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laboratory performing the test is usually used to define anaemia. There is no reason why a 'mild' anaemia should be less indicative of important disease than 'severe' anaemia.¹

Microcytosis (mean corpuscular volume (MCV) lower than normal range) is characteristic of chronic iron deficiency, but can occur in other conditions such as thalassaemia and anaemia of chronic disease. The red cell distribution width (RDW) is also a useful marker to assess when looking for GIT disease as it may be raised, with a normal MCV, in patients with a combined deficiency (e.g. folate or vitamin B₁₂ combined with iron deficiency) in malabsorptive states (e.g. coeliac or Crohn's disease).

Serum ferritin is the most powerful test for iron deficiency. A ferritin <15 µg/l is diagnostic of iron deficiency. If ferritin is >100 µg/l, iron deficiency is almost certainly not present even in patients with concurrent chronic inflammation, malignancy or hepatic disease.

Further tests to define iron deficiency are only useful when doubt still remains as to the presence of iron deficiency, and advice from a haematologist should be sought if necessary.

The need for investigation of patients with iron deficiency, but without anaemia, has not been assessed in clinical trials. However, in all patients over 50, colon cancer screening is recommended and if iron deficiency is recognised in this group, this further strengthens this recommendation.

Investigations

History

Obtaining a good dietary history is important, but diet should not be thought to be the cause of anaemia until a full GIT work-up has excluded other causes. The presence of upper and lower GIT symptoms should be documented, although they rarely correlate with investigations. A history of weight loss, GIT bleeding (haematemesis, melaena, haematochesia), dysphagia, change of bowel habits or a positive family history of GIT cancer are considered 'alarm' symptoms and necessitate urgent gastrological referral. The use of aspirin and NSAIDs should be noted and stopped if possible.

The use of warfarin should not be considered a cause of iron deficiency and its use should not defer further investigation.

A family history of haematological disorders (e.g. thalassaemia), telangiectasias and bleeding disorders should also be sought. Recurrent epistaxis may point to hereditary telangiectasia (Osler-Weber-Rendu syndrome).

Examination

Careful examination, including rectal examination, although seldom contributory, may reveal important signs pointing to iron deficiency (angular stomatitis (Fig.1), koilonychia) or GIT blood loss (telangiectasia under the tongue, rectal mass, etc.). Urine dipstix should also be performed as renal cell carcinoma has been shown to be an important cause of iron deficiency anaemia, particularly in men over 50.³

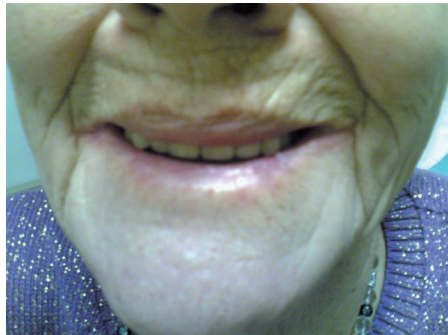


Fig. 1. Angular stomatitis: 78-year-old woman with long-standing history of unexplained iron deficiency anaemia and osteoporosis with angular stomatitis. The patient was diagnosed with coeliac disease after duodenal biopsy revealed complete villous atrophy and the patient had a positive anti-endomysial antibody test.

Gastrointestinal investigations

Unless there is an obvious history of significant non-GIT blood loss, gastrointestinal investigation should be considered in all patients with confirmed iron deficiency anaemia. The incidence of malignancy in this group of patients has been reported to be as high as 13%.¹ Both upper and lower investigations should be performed as the incidence of dual pathology is as high as 15% in some studies.¹ There is debate as to the order of investigation but this may depend on local availability of services.

In the setting of iron deficiency anaemia, small-bowel biopsy from the second or third part of the duodenum at the time of gastroscopy should be performed to exclude the possibility of coeliac disease. *H. pylori* colonisation may impair iron uptake and increase iron loss. Eradication of *H. pylori* may reverse anaemia and therefore it should be sought and eradicated if present.¹ In patients referred to the Johannesburg medical GI clinic, upper GI malignancy (gastric

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cancer, oesophageal cancer or lymphoma) was diagnosed in 3.6% of patients and coeliac disease in 1.1% of patients with confirmed iron deficiency anaemia.² If the patient is unable to have upper endoscopy, a barium meal should be performed in combination with serological tests for coeliac disease (IgA anti-endomysial antibody or IgA anti-tissue transglutaminase).

Unless malignancy or coeliac disease is diagnosed, the lower GIT should also be investigated. Colonoscopy is the procedure of choice for lower GIT investigation as it has the advantage of demonstrating angiodysplasia (Fig. 2) and allows for biopsy and other interventions as required (e.g. polypectomy). If possible this should be performed at the same time as the gastroscopy.

If colonoscopy is not available, double contrast barium enema (preferably with sigmoidoscopy and at least careful digital rectal exam) is an acceptable alternative. CT or MRI colonoscopy have not been assessed for this indication. However, if colonoscopy is incomplete or unable to be performed CT or MRI colonoscopy may be an alternative.

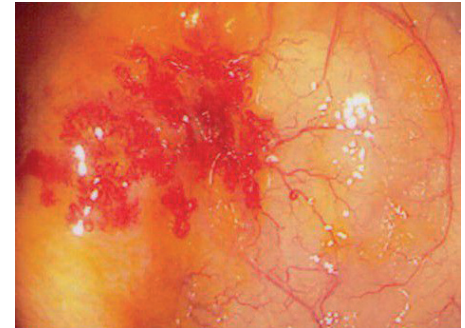


Fig. 2. Angiodysplasia: Patient referred for second opinion for further investigation of unexplained iron deficiency after previously reported 'normal' gastroscopy and colonoscopy. On repeat colonoscopy, after good bowel preparation, multiple angioectasias were noted in the caecum.

Faecal occult blood testing has little to add in the initial investigation of patients with iron deficiency anaemia as GIT investigation should still be performed even if the result is negative!

Lower GIT malignancy was diagnosed in nearly 5% of all patients with confirmed iron deficiency anaemia referred to the Johannesburg medical GIT department,² but

Table I. Some GIT causes of asymptomatic iron deficiency anaemia and prevalence as percentage of total

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%
Malabsorbtion	
Common	
Coeliac disease	4 - 6%
Gastrectomy	<5%
<i>H. pylori</i> colonisation (on its own)	<5%
Uncommon	
Bowel resection	<1%
Bacterial overgrowth	<1%

Peptic ulcer disease and inflammatory bowel disease are common causes of GIT bleeding, but are normally symptomatic

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has been reported to be as high as 29% in men and postmenopausal women in some studies.³

Some GIT causes of asymptomatic iron deficiency anaemia and their prevalence as a percentage of the total are given in Table I.

Further studies

If upper and lower GIT investigations are negative, patients should be considered for abdominal imaging. Renal cell carcinoma has been shown to be an important cause of occult bleeding in men in particular, occurring more frequently than rectal, oesophageal or small-bowel tumours in a large UK study in patients with asymptomatic iron deficiency anaemia.³

Unless the iron deficiency anaemia is transfusion dependent, or there has been visible blood loss, further studies are not normally required.⁴ Dietary deficiencies should be corrected, NSAIDs stopped and haemoglobin monitored. If the haemoglobin is not maintained and endoscopy has not been previously performed (e.g. barium meal and enema performed), or if it is suboptimal due to inadequate bowel prep or an inexperienced operator, repeat gastroscopy and colonoscopy should be performed (Fig. 3). The repeat procedures should ideally be done after optimal preparation and by an experienced operator to detect difficult-to-identify pathology, e.g. Cameron ulcers within a hiatus hernia, or a small angiodysplastic lesion. Once the upper and lower GIT and renal tract have been 'cleared', patients with transfusion-dependent anaemia or overt obscure GIT bleeding should be referred for small-bowel investigation.⁴

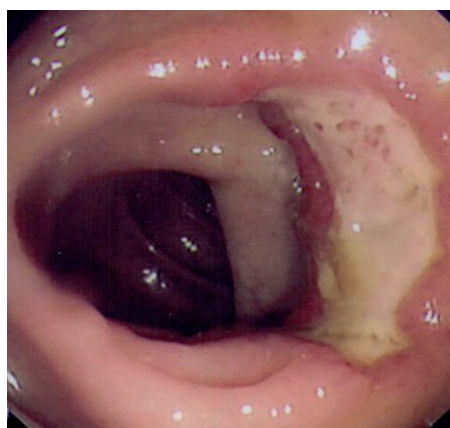


Fig. 3. Crohn's disease: A 28-year-old man with unexplained iron deficiency anaemia was referred for further evaluation after a previous negative gastroscopy, colonoscopy and an open intraoperative small bowel enteroscopy with no cause established. The patient then underwent a red cell scan that revealed pooling of blood in the right colon. A repeat colonoscopy revealed large punched-out ulcers in keeping with colonic Crohn's disease in the ascending colon that appeared to have been missed on initial colonoscopy, probably because the ascending colon was not reached.

Since the introduction of video capsule endoscopy (VCE) and double balloon endoscopy (DBE) there has been a major paradigm shift in the work-up of these challenging patients. In 2000 the American Gastroenterology Association proposed progressive testing with bleeding scans and angiography for patients with active or overt bleeding. Push enteroscopy, enteroclysis or small-bowel follow-through studies were recommended for patients without overt bleeding, and intraoperative enteroscopy for patients with ongoing unexplained blood loss. The average costs were estimated to be greater than \$33 000 (R230 000) per patient without a diagnosis being made in the majority!⁴ This is still the route being followed in most state hospitals in South Africa without access to video capsule or double balloon endoscopy. In private practice VCE and DBE are now available in some centres and are the recommended next line of investigation.

'Bidirectional' DBE has recently been shown to be as sensitive and specific as VCE in iron deficiency anaemia, can be done on an outpatient basis and allows for intervention at the time of endoscopy.⁵ DBE is however invasive and very time consuming. VCE is therefore the recommended first-line investigation, if available, for patients with unexplained transfusion-dependent iron deficiency or overt obscure GIT bleeding.⁶ If a treatable lesion is found or biopsy is required the patient should be referred for DBE.

If video capsule is not available, DBE is considered an acceptable alternative. It should also be performed if there is an ongoing iron deficiency anaemia or bleeding not explained by capsule endoscopy.

Special considerations

Co-morbidities

Appropriate investigations in patients with severe co-morbidities should be carefully considered, especially if the results would not change further management. However, iron deficiency anaemia should never be ascribed to 'old age' on its own.

Premenopausal women

Iron deficiency is common in this group, occurring in up to 10%. Menstrual blood loss, pregnancy and breast feeding are usually responsible. It has been shown that history is unreliable in quantifying menstrual losses. There are few data on the yield of GI investigation in menstruating women. The British Society of Gastroenterology Guidelines state that all patients be serologically screened for coeliac disease, and patients over 50 should be investigated as one would with males or postmenopausal

females.¹ If patients have GIT symptoms, gastroscopy with small-bowel biopsy should be performed. Colonoscopy should only be undertaken if alarm symptoms are present or if iron deficiency persists despite oral iron therapy and correction of reversible causes (e.g. diet, NSAIDs).

Coeliac disease

Coeliac disease is considered an autoimmune disease.⁷ It is due to the body's genetically predetermined response to an environmental trigger – gluten (found not only in wheat, but also in rye, barley and oats in small amounts). As many as 95% of coeliacs are HLA DQ2 positive and the rest are HLA DQ8 positive. In a patient with coeliac disease, gluten causes a strong entero-lymphocytic response, resulting in destruction of villi, especially in the proximal small bowel, seen on histology as varying degrees of villous atrophy and lymphocytic enteritis characterised by intraepithelial lymphocytes. The small bowel may look normal endoscopically; hence the need for small-bowel biopsy. Loss of absorptive surface area may result in asymptomatic malabsorption of products usually absorbed predominantly in proximal small bowel such as iron and calcium, resulting in anaemia and osteoporosis. Chronic lymphocytic activation may also result in enteropathy-associated T-cell lymphoma. The best serological test to screen for coeliac disease is an IgA anti-endomysial (AEM) or IgA anti-tissue transglutaminase (tTG) and not anti-gliadin antibodies.

Video capsule endoscopy

VCE received FDA approval in 2001. The video capsule is usually easily swallowed and propelled by peristalsis. It is performed on an outpatient basis. The capsule has a short focal length and narrow aperture to increase depth of field and transmits 2 images per second. 'Video' images are transmitted to 8 receivers (size of ECG electrodes) attached to the body. This permits capture of images and calculation of capsule position. The images are stored on a small portable recorder carried on a belt. This system allows for over 7 hours of recording images of the GIT and typically takes between 45 minutes and 2 hours to review once downloaded onto a computer. Capsule endoscopy can provide images of the entire small bowel, but does not allow for any intervention on its own.⁸

Double balloon endoscopy

DBE was developed in 2001 as a method of small-bowel endoscopy. Antegrade (*ab oro* (Fig. 4)) and retrograde (*ab ano* (Fig. 5)) insertion can be combined and allows for visualisation of the entire small bowel. This usually requires conscious sedation and is performed in two sessions. DBE enables endoscopic intervention such

as biopsy, polypectomy, stricture dilatations, argon plasma coagulation of angiodysplasia or tattoo, but is very time consuming, requires a high level of staffing and an experienced well-trained endoscopist.⁵

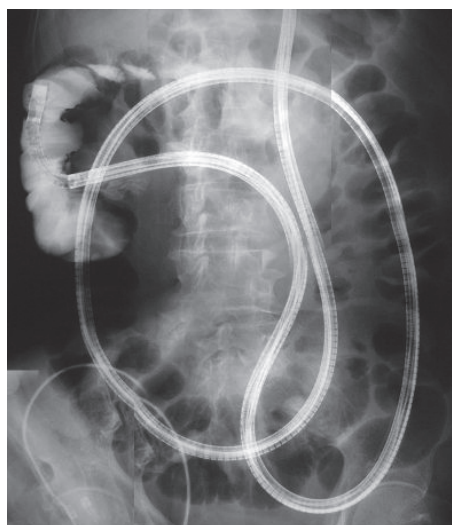


Fig. 4. Double balloon endoscopy: X-ray of the abdomen in a patient undergoing ab oro DBE. Note that the tip of the scope has been advanced all the way into the caecum.

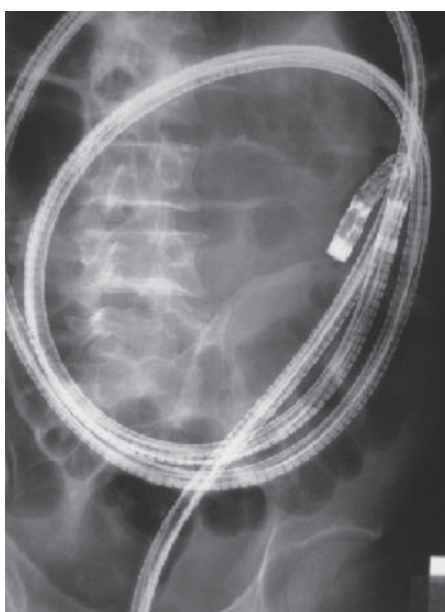


Fig. 5. Double balloon endoscopy: X-ray of the abdomen in a patient undergoing ab ano DBE.

Conclusion

Iron deficiency anaemia is common and should never be ignored or treated empirically without establishing the probable cause. In men and postmenopausal women,

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GIT evaluation is imperative to rule out upper and lower GIT malignancy but other causes should not be overlooked. In patients with ongoing GIT blood loss or unexplained transfusion-dependent iron deficiency anaemia, further small-bowel evaluation is mandatory.

Acknowledgements

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In a nutshell

- Iron deficiency anaemia is common.
- Ferritin is the most powerful predictor of iron deficiency.
- GIT pathology is the most important cause of iron deficiency in postmenopausal women and in men.
- In women > 50 years or in men, iron deficiency anaemia should never be treated empirically without both upper and lower GIT evaluation.
- In patients with overt GIT bleeding or transfusion-dependent iron deficiency unexplained on gastroscopy and colonoscopy, small-bowel evaluation is indicated.

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