Common causes of iron deficiency anaemia in gastroenterology patients

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Abstract

Gastroenterological disorders frequently lead to anaemia as a result of blood loss, inflammation, malabsorption or drug therapies. With malignancy or inflammatory bowel disease, the causes are often multifactorial. Aside from iron deficiency, other conditions resulting in vitamin B_{12} or folate deficiency can lead to anaemia. Here, coeliac disease, inflammatory bowel disease and surgical resection are particular risk factors. The approach to anaemia in the gastroenterology patient should focus on establishing and managing the underlying cause while supplementing any deficiencies to correct the anaemia.

Keywords Anaemia; intravenous iron; iron deficiency anaemia; MRCP; vitamin B_{12} and folate

Key points

- Anaemia is very common in gastroenterology and often caused by iron deficiency
- Management of the underlying cause of anaemia should occur alongside correction of iron, vitamin B_{12} or folate deficiencies
- Investigation of the cause of iron deficiency anaemia should be structured and considered in accordance with national guidelines
- Intravenous iron supplementation is often superior to oral supplementation because of its greater efficacy and tolerability

Introduction

Anaemia affects nearly a quarter of the worldwide population and is highly prevalent in gastroenterology patients. In the UK, iron deficiency anaemia (IDA) affects an estimated 3% of men and 8% of women, and forms 4–13% of gastroenterology referrals.[1] Correcting anaemia can lead to improved quality of life and increased activity levels while reducing healthcare utilization.[1] Anaemia often results from iron, folate or vitamin B_{12} deficiency, because of enteric blood loss, malabsorption or dietary insufficiency. This article reviews the pathogenesis of anaemia, with a particular focus on IDA, highlighting the common causes of IDA and examining current evidence for its management.

Iron absorption and regulation

Optimal iron homeostasis is an integral part of normal erythropoiesis, but iron is also an important co-factor in a number of other essential metabolic processes in humans. A series of intricate pathways regulate iron metabolism, and there is now a clear understanding of the pathogenesis behind IDA.

In healthy individuals, total body stores of iron are 4–5 g. The daily requirement of iron for haemoglobin synthesis is 25–30 mg, with 90% being recycled from erythrocytes and 10% absorbed from the diet, predominantly in the duodenum. Much of the uptake, storage and reuse of iron is regulated by the liver hormone hepcidin. Within the enterocytes, iron is also regulated by its storage protein ferritin and the transmembrane exporter ferroportin. The normal absorptive pathway is described and illustrated in Figure 1. Absorption of iron through this pathway is impaired in diseases effecting the gastrointestinal (GI) tract.

Ferritin can be upregulated in chronic inflammation, causing an increase in intracellular storage and a block of absorption. In addition, inflammation drives the release of hepcidin from the liver, which acts as the regulator of the central iron stores by binding to ferroportin, thus causing a loss of function in enterocytes. This downregulation in ferroportin function in enterocytes causes a reduction in duodenal iron absorption. Hepcidin is also regulated through plasma iron levels and the transporter protein transferrin. Transferrin acts as a ligand for hepatocellular receptors involved in expression of the *HAMP* gene, responsible for encoding hepcidin.

Anaemia is defined by the World Health Organization as a haemoglobin concentration <120 g/litre in women, and <130 g/litre in men. Iron deficiency results in a hypochromic microcytic anaemia, defined by a low mean cell volume <80 fl and a low mean cell haemoglobin (Table 1). In the setting of anaemia, a ferritin concentration <15–100 micrograms/litre and a transferrin saturation <16–20% are considered diagnostic of iron deficiency.

Mechanical or inflammatory causes of iron deficiency anaemia

The differential diagnoses of occult blood loss from the GI tract are extensive and should form the focus of investigating unexplained IDA (Table 2). In the upper GI tract, non-variceal bleeding can occur in the form of oesophagitis, gastritis or ulceration. In addition, hiatus hernias themselves carry, on average, a 20% incidence of IDA because of ulceration and

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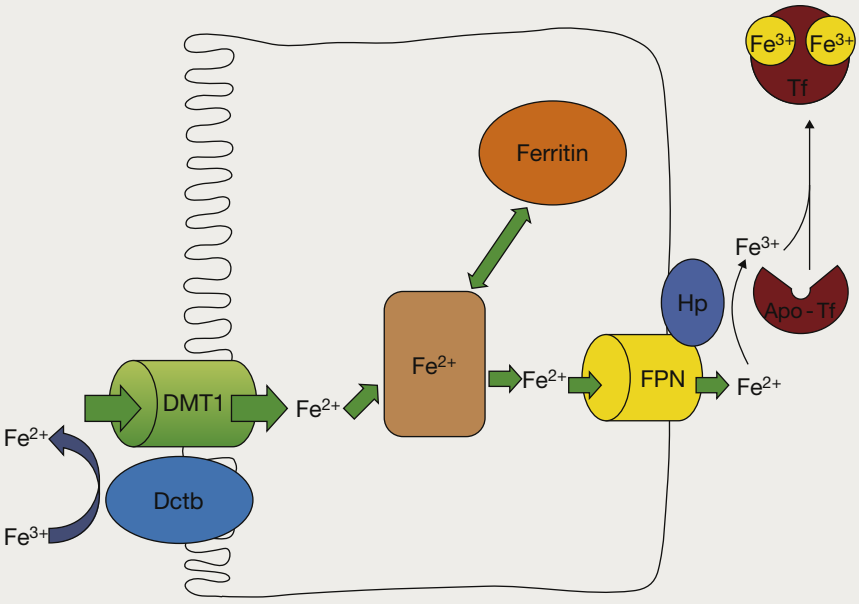
Normal pathway for absorption of iron



Ferroreductase converts ferric iron (Fe^{3+}) to ferrous iron (Fe^{2+}) before transporting it into enterocytes via the divalent metal transporter 1 (DMT1). Ferroportin (FPN) then acts to transport the Fe^{2+} across the basolateral surface of the enterocytes and into the plasma. Alternatively, Fe^{2+} can be incorporated into ferritin. Hephaestin (Hp) acts to convert Fe^{2+} to Fe^{3+}.

Dctb, duodenal cytochrome B; Tf, transferrin; Apo-Tf, apo-transferrin.

Source: Reproduced with permission from Padmanabhan H, Brookes MJ, Iqbal T. Iron and colorectal cancer: evidence from *in vitro* and animal studies. *Nutr Rev* 2015; **73**: 308–17.

Figure 1

bleeding in the linear folds of the stomach (Cameron lesions) as it is constricted by the thoracic diaphragm.

The association between non-steroidal anti-inflammatory drugs (NSAIDs) and GI bleeding is well established. Non-selective NSAIDs pose the highest risk of GI injury. In anaemic patients with a clear history of NSAID use, capsule endoscopy can be warranted in the absence of lesions being detected during gastroscopy or colonoscopy. Even low-dose aspirin has been

Blood indices in common causes of anaemia in gastroenterology

	MCV (80–100 fl)	MCH (27–32 pg)	MCHC (30–40 mg/dl)	Iron (10–30 μmol/litre	TIBC 47–70 mmol/litre	TSAT (16–50%)	Ferritin (15–300 micrograms/litre)	Appearance
Iron deficiency anaemia	↓	↓	↔/↓	↓	↑	↓	↓	Microcytic hypochromic
Anaemia of chronic disease	↔	↔/↓	↔	↔/↓	↓	↓	↔/↑	Normocytic normochromic
Pernicious anaemia (vitamin B_{12} deficiency)	↑	↑	↔	↔/↑	↔/↑	↔/↑	↔/↑	Macrocytic normochromic
Folate deficiency anaemia	↑	↑	↔	↔/↑	↔/↑	↔/↑	↔/↑	Macrocytic normochromic

↑ increased; ↑ decreased; ↔ normal; MCH, mean cell haemoglobin; MCHC, mean cell haemoglobin concentration; MCV, mean cell volume; TIBC, total iron binding capacity; TSAT, transferrin saturation.

Table 1

Causes of occult gastrointestinal bleeding

Inflammatory/mechanical trauma	• Reflux oesophagitis • Gastric/duodenal ulcer • Cameron lesions • Erosive gastritis • Inflammatory bowel disease • Whipple's disease • Meckle's diverticulum • Coeliac sprue
Mass lesion	• Carcinoma • Large polyps
Vascular	• Angiodysplasia • Portal hypertensive gastropathy • Gastric antral vascular ectasia • Blue rubber bleb syndrome
Infectious	• Hookworm • Ascariasis • Strongyloidiasis • Tuberculous enterocolitis
Miscellaneous	• Long-distance running • Haemoptysis

Table 2

found to increase faecal blood loss by 2–4 times from baseline compared with placebo.[2]

Helicobacter pylori infection has been linked to >50% of refractory IDA. In meta-analysis, eradication therapy combined with iron supplementation has been shown to significantly increase haemoglobin, serum iron and serum ferritin concentrations compared with iron supplementation alone.[3] The mechanism of *H. pylori*-induced IDA is multifactorial. Aside from blood loss resulting from gastric erosions, *H. pylori* also uses iron for growth and proliferation. Furthermore, *H. pylori* helps to drive hepcidin synthesis and reduces the gastric secretion of ascorbic acid, thus disturbing iron uptake.[3]

Less commonly, autoimmune atrophic gastritis can affect iron absorption through a progressive loss of parietal cells. Recent evidence has shown that, in addition to vitamin B_{12} malabsorption, the resultant achlorhydria is an independent cause of IDA.[4]

Malignancy

Anaemia is highly prevalent in colorectal cancer, with around 40–60% of patients being anaemic at presentation. Studies have shown that tumour site (right colon) and increasing tumour size, but not clinical stage or histological type, are risk factors for anaemia.[5] In addition to occult or overt blood loss, malignancy produces a proinflammatory state leading to cytokine release; this in turn triggers hepcidin-mediated iron sequestration and restricted erythropoiesis.

In surgical patients, preoperative anaemia is an independent risk factor for complications and postoperative length of stay. Perioperative allogenic red blood cell transfusion (ARBT) is an option for these patients, but current evidence suggests that ARBT may, through changes in immunomodulation, be linked to adverse perioperative outcomes and even tumour recurrence (see Further reading). Recent studies have focused on intravenous iron as an alternative to ARBT in these patients. In the context of colorectal cancer, intravenous iron has been found to be more effective than oral iron in treatment of preoperative anaemia (see Further reading).

Evidence of colonic pathology in anaemic patients should not preclude investigation of the upper GI tract because there is a small but not insignificant incidence of synchronous upper and lower GI tumours. Gastrointestinal stromal tumours (GISTs) are another important cause of IDA caused by chronic blood loss. The treatment of GISTs with tyrosine kinase inhibitors can worsen iron deficiency.

Guidance for investigating patients presenting with IDA and suspected malignancy, with or without overt GI blood loss, is outlined in Table 3. Further information can be reviewed in the guidelines produced by the British Society of Gastroenterologists.[1]

Intestinal failure

Intestinal failure results in an inability to adequately absorb nutrients because of obstruction, motility dysfunction, major surgical resection or a disease-induced disorder of absorption.

National Institute for Health and Care Excellence guidelines for the investigation of anaemia in adults with suspected cancer

Investigation findings and specific features	Possible cancer	Recommendation
Anaemia (IDA), age ≥60 years	Colorectal	2WW pathway
Anaemia (IDA, unexplained), rectal bleeding, age <50 years	Colorectal	2WW pathway
Anaemia (IDA) without rectal bleeding, age <60 years	Colorectal	Offer FOB
Anaemia (even in the absence of IDA) without rectal bleeding, age ≥60 years	Colorectal	Offer FOB
Haemoglobin levels low with upper abdominal pain, age ≥55 years	Gastroesophageal	Upper GI endoscopy

2WW, 2-week-wait pathway; FOB, faecal occult blood test; GI, gastrointestinal; IDA, iron deficiency anaemia.

Source: NICE (2015) Suspected cancer: recognition and referral (NG12). National Institute for Health and Care Excellence. Published June 2015, last updated June 2017. Accessed via https://www.nice.org.uk/guidance/ng12

Table 3

In conditions such as Crohn's disease, the causes of anaemia resulting from intestinal failure are often multifactorial.

Chronic mucosal inflammation can disrupt erythrocytosis through disturbance of iron regulation. During an active flare-up of the disease, blood loss can exceed duodenal iron absorption, and still active duodenal or jejunal Crohn's disease can impede iron and folate uptake. In addition, major surgical resection can result in 'short-gut syndrome', limiting the absorptive capacity for nutrients. If surgery is indicated, terminal ileal resection is most frequently required and can lead to anaemia as a consequence of vitamin B_{12} malabsorption. Consideration should also be given to patients with inflammatory bowel disease (IBD) who have undergone ileo-anal pouch formation following a previous colectomy. Here, inflammation and blood loss from pouchitis can result in IDA.

The treatment of IBD can itself contribute to anaemia. Drugs such as 6-mercaptopurine and azathioprine have a myelosuppressive effect, while sulfasalazine and 5-aminosalicylic acid can cause folate deficiency and, to a lesser degree, haemolysis.

Because of its GI adverse effects, oral iron is generally poorly tolerated in patients with IBD, particularly in those with quiescent disease. The European Crohn's and Colitis Organisation recommends using intravenous iron preparations in such cases (see Further Reading). Patients with adequately treated disease can be offered iron erythropoiesis-stimulating agents if they fail to respond to oral or intravenous iron.

Surgical resection

Patients who have undergone surgical resection of the upper GI tract for either benign or malignant pathology are at risk of developing anaemia and should be monitored and offered supplementation accordingly. Post-gastrectomy anaemia is a well-recognized entity resulting from disturbance of iron, folate and vitamin B_{12} absorption. Bariatric patients who have undergone weight loss procedures such as Roux-en-Y bypass, sleeve gastrectomy or bilio-pancreatic diversion/duodenal switch procedures are also at risk. Blood loss from anastomotic ulceration is a rare cause of anaemia.

Evidence suggests that oral iron preparations have limited efficacy in post-surgical bariatric patients, and intravenous iron can be more useful.

Angiodysplasia

Blood loss from angiodysplasia frequently causes IDA. The multiplicity of lesions often means that it is problematic to identify and treat the bleeding. Prevalence appears to increase with age and is second only to diverticular disease as the leading cause of rectal bleeding in the over-60s. Around 10% of patients present with an acute haemorrhage, with chronic occult blood loss occurring in the rest.

Coeliac disease

Anaemia is common in coeliac disease and is often the only detectable sign at presentation. Reports suggest that IDA occurs in 30–70% of the coeliac population. Biopsy-proven coeliac disease has an average prevalence of 1 in 31 individuals with IDA (see Further reading), so coeliac serology should be considered for all anaemic patients. Disease localized to the proximal small intestine can impair iron absorption because of villous atrophy, and occult blood loss can also be a factor in the development of anaemia.

When instituting iron therapy, the importance of disease control and dietary modification should be emphasized to facilitate adequate iron absorption. Indeed, individuals with coeliac diseases are often unresponsive to oral iron, so intravenous iron should be their first-line management. Furthermore, progression of the condition can also lead to vitamin B_{12} and folate deficiency, which can require parenteral supplementation or 3-monthly hydroxocobalamin injections.

Parasitic infections

Worldwide, intestinal parasitic infections remain a common cause of anaemia. Hookworm infections cause iron loss from intestinal mucosal inflammation, whereas roundworm infection can cause mucosal bleeding and dysentery, leading to intestinal malabsorption. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 62-year-old man presented in primary care with fatigue and an altered bowel habit. He had a past history of hypertension and mild asthma. He was an ex-smoker.

On clinical examination, abdominal examination was unremarkable, and digital rectal examination was normal.

Investigations

- Haemoglobin 91 g/litre (130–180)
- Mean cell volume 72 fl (80–96)

What is the most appropriate next step in his management?

A. Start oral iron replacement and review in 4 weeks
B. Refer for routine colonoscopy
C. Faecal occult blood testing
D. Two-week-wait referral
E. Stool sample for culture

Question 2

A 38-year-old woman with a diagnosis of coeliac disease was being treated by her GP for iron deficiency anaemia. Before commencing iron replacement therapy, her GP requested a repeat of her blood tests for review.

Which of the following is increased in iron deficiency anaemia?

A. Ferritin
B. Mean cell volume
C. Total iron binding capacity
D. Mean cell haemoglobin concentration
E. Mean cell haemoglobin

Question 3

A 48-year-old man presented with three flare-ups of his Crohn's disease characterized by increased stool frequency and some bloody diarrhoea over the previous 4 months. He had been treated with a course of corticosteroids. He had had no previous abdominal surgery.

Investigations

- Haemoglobin 81 g/litre (130–180)
- Serum iron 8 micromol/litre (12–30)
- Mean cell volume 72 fl (80–96)
- Ferritin 290 microgram/litre (15–300)
- Transferrin saturation 21% (15–50%)
- C-reactive protein 51 mg/litre (<10)

What is the most likely diagnosis:

A. Iron deficiency anaemia (IDA)
B. Pernicious anaemia
C. Anaemia of chronic disease (ACD)
D. Mixed anaemia (IDA and ACD)
E. Drug-induced haemolytic anaemia