Iron deficiency anaemia: a review of diagnosis, investigation and management

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Iron deficiency anaemia (IDA) is the most common form of anaemia worldwide. In men and postmenopausal women the commonest cause of IDA is blood loss from lesions in the gastrointestinal tract, making it a common cause of referral to gastroenterologists. Causes of IDA relate either to blood loss or iron malabsorption. After confirmation with laboratory tests, gastrointestinal evaluation is almost always indicated to exclude gastrointestinal malignancy. Specific patient groups such as premenopausal women, patients with low-normal ferritin and iron-deficient patients without anaemia may need an individualized approach. A small proportion of patients have recurrent or persistent IDA despite negative standard endoscopies. These patients with obscure gastrointestinal bleeding usually require evaluation of the small bowel with capsule endoscopy or double balloon enteroscopy. Treatment should involve prompt iron replacement plus diagnostic steps directed towards correcting the underlying cause of IDA. Oral iron replacement is cheap and effective, but parenteral (intravenous) therapy may be required due to intolerance, noncompliance or treatment failure with oral therapy. *Eur J Gastroenterol Hepatol* 24:109–116 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Iron deficiency anaemia (IDA) is the most common form of anaemia worldwide and is estimated to be the cause of up to 50% of anaemia cases [1,2]. In the developed world, iron deficiency occurs in up to 11% of women aged 20–49 years and 2–4% of men over the age of 50 years. IDA is present in 1–2% of adults [3].

In men and postmenopausal women the commonest cause of IDA is blood loss from lesions in the gastrointestinal (GI) tract [4–10], making it a common cause of referral to gastroenterologists [4]. A substantial proportion of these lesions are either cancerous or precancerous. In this study, we review the aetiology, diagnosis, evaluation and treatment of IDA.

Iron transport and metabolism

The average adult iron intake is 10–15 mg per day of which 1–2 mg is absorbed by duodenal enterocytes. Ingested iron then undergoes enzymatic reduction from ferric iron (Fe^{3+}) to the more readily absorbed ferrous iron (Fe^{2+}) by brush border ferrireductase with the help of low gastric pH. Divalent metal transporter 1 (DMT1) on duodenal epithelium transfers iron across the apical membrane where it is either transferred across the basolateral membrane to reach plasma bound to transferrin or stored as ferritin and eventually excreted as the enterocyte is sloughed [11].

The absorption of intestinal iron is tightly regulated by at least three regulatory mechanisms: a dietary regulatory, a stores regulator and an erythropoietic regulator. These control the expression of hepcidin, a key peptide in iron homeostasis through its control on transporters such as DMT1 and ferroportin [11,12].

When the loss of iron from the body exceeds its ability to absorb dietary iron, a negative iron balance ensues and eventually affects erythropoiesis causing IDA. In the developed world, a negative iron balance is primarily due to blood loss (overt or occult) and/or GI malabsorption (Table 1).

Causes

Blood loss

Blood loss greater than 5–10 ml per day exceeds the amount of iron the gut can absorb from a normal diet [5,7]. Patients with gastroduodenal blood loss of up to 100 ml per day may still have normal appearing stools [13].

From previous studies of heterogenenous populations, the rate of GI pathology in patients with IDA varies from 43 to 86% [4,6,7,10,14–19]. Predictive factors for finding a bleeding lesion responsible for IDA on endoscopy include higher age, positive faecal occult blood test (FOBT), absence of lower GI tract symptoms (nonepigastric abdominal pain, diarrhoea, constipation) and mean corpuscular volume (MCV) of less than 60 fl [19,20]. The most common lesions are benign erosive lesions in the upper GI tract, which account for 39–57% of all GI pathologies found [4,6,7,10]. Of these, peptic ulcers (gastric and duodenal) were the most common [4,6]. There are conflicting data regarding the use of aspirin or NSAIDs and erosive lesions in the upper GI tract, a

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Table 1 Causes of iron deficiency anaemia

Causes of iron deficiency
Increased iron loss (gastrointestinal)
Peptic ulcer (gastric, duodenal, Cameron's)
Cancer (gastric, oesophageal, small bowel, colonic)
Vascular abnormalities (angiodysplasia, GAVE, HHT)
Inflammatory bowel disease
Colonic or gastric polyps
Gastritis, oesophagitis
Parasitic infections (hookworm)
Increased iron loss (nongastrointestinal)
Menorrhagia
Recurrent epistaxis
Urinary blood loss
Chronic intravascular haemolysis
Regular blood donation, phlebotomy
Iron malabsorption
Coeliac disease
Previous gastrectomy
Achlorhydria and hypergastrinaemia
Increased demand for iron
Adolescence
Pregnancy
Erythropoeitin therapy
Inadequate diet intake (vegetarians, vegans)

GAVE, gastric antral vascular ectasia; HHT, hereditary haemorrhagic telangiectasia.

correlation found in some studies [10,19] but not in others [6,7,15,17]. The most common lower GI lesion is carcinoma of the colon accounting for 42–69% of lesions seen on colonoscopy [6,10,14,15,20]. Although right-sided colon cancers have traditionally been thought to be a leading cause of IDA more so than cancers of the left colon and rectum, literature shows that the ratio of right-sided-to-left-sided colon cancers is highly variable, that is, from 1 : 1 to as high as 9 : 1 [6,7,10,15,17].

The prevalence of GI malignancy in patients with IDA is reported to be 6–13% [4,6,7,16–20], although some studies report rates as high as 29–51% [16,17]. Comparatively, GI malignancies are present in only 0.2% of patients with normal haemoglobin and iron saturation [18]. Several studies have consistently reported older age (> 50 or 60 years), male sex and lower haemoglobin level (< 8 or 9 g/dl) to be significant predictive factors for GI malignancy in IDA patients while lower MCV (< 70 fl), lower serum ferritin ($\leq 10\,\mu g/l$) and lactate dehydrogenase greater than 250 U/l ran a higher risk of malignancy in some studies but not in others [16,17,20]. Interestingly positive FOBT, family history of first-degree relative with GI cancer and symptoms of weight loss, abdominal pain or change in bowel movement were not predictive for GI malignancy [16,17,20].

Decreased absorption

GI malabsorption should also be considered as a potential cause of IDA especially when no source of GI bleeding is found and when there is refractoriness to oral iron therapy. Nonbleeding GI conditions that may cause abnormal iron absorption, and hence IDA, are seen frequently in up to 50% of patients, but often overlooked [21].

It is reported that occult coeliac disease occurs in 5–6% of adults with IDA [21,22]. The cause of iron deficiency from coeliac disease is often thought to be due to malabsorption because the main site of iron absorption (duodenum) is always involved in coeliac disease [22,23]. However, concomitant occult GI bleeding (detected by FOBT) may be present in up to 47% of all coeliac patients and in 54% of those with total villous atrophy [23]. Although subclinical coeliac disease presenting with IDA is uncommon [22,23], it is found in 5% of IDA patients and in 8.5% of those with IDA unresponsive to oral iron therapy [22]. Serological testing and small bowel biopsies should therefore be performed in patients with IDA not due to bleeding, especially if they are unresponsive to oral iron therapy [22,24].

The association between *Helicobacter pylori* infection and reduced iron absorption is well established [25–27]. A meta-analysis of seven observational epidemiologic studies found at least a two-fold-increased risk of IDA among individuals infected with *H. pylori* compared with noninfected individuals [27]. However, as pointed out by Bini [28], although studies support a possible causative role of *H. pylori* in IDA, a temporal relation needs to be demonstrated before causality is established.

IDA is a well-recognized consequence after gastric bypass surgery and partial gastrectomy [29–31]. This occurs due to bypass of the duodenum (the major site of iron absorption) and reduced availability of gastric juice (which plays an important role in iron absorption), respectively.

With the weight of the above evidence, patients with IDA who are poorly responsive to oral iron or have no evidence of a bleeding GI lesion should be routinely evaluated for coeliac disease, *H. pylori* infection and atrophic gastritis with gastric and duodenal biopsies.

Uncommon causes

Occult blood loss can also come from outside the GI tract including the renal tract (haematuria) or the lung (pulmonary haemosiderosis). Rarely chronic intravascular haemolysis or treatment with erythropoietin in chronic renal disease may result in IDA. Congenital iron deficiencies due to atransferrinaemia or genetic defects of DMT1 and other iron transporters are exceedingly rare [12]. More recently, germline mutations in the TMPRSS6 gene, which encodes a transmembrane serine protease responsible for regulation of hepcidin have been shown to cause iron refractory iron deficiency anaemia [32].

Diagnosis of iron deficiency anaemia

History and examination

The clinical presentation of IDA can range from being completely asymptomatic (found on routine testing) to varying degrees of weakness, fatigue, irritability, headache,

poor exercise tolerance and work performance [2]. Pica may be seen in some cases of iron deficiency with pagophagia (irresistible appetite for ice) being quite specific for iron deficiency [33]. Ask about overt blood loss as well as symptoms of GI disease (abdominal pain, change in bowel habit, weight loss and dysphagia). Use of medications such as aspirin or NSAIDs should also be noted. A family history of GI malignancy, haematological disorders and bleeding disorders (e.g. hereditary haemorrhagic telangiectasia) is important, as is the patient's ethnicity when suspecting thalassemia or coeliac disease.

On examination, patients may have pallor (related to anaemia), cheilosis or atrophic glossitis. Severe, longstanding iron deficiency presenting as Plummer–Vinson syndrome (postcricoid dysphagia, IDA, oesophageal webs), koilonychia, blue sclerae and chlorosis have become extremely rare [12]. Urine testing for microscopic haematuria and a rectal examination should be included in the physical examination [17,34].

Laboratory diagnosis

The World Health Organization defines anaemia as the level of haemoglobin below 13 g/dl in males over 15 years of age and below 12 g/dl in nonpregnant women over 15 years of age [2]. Although there is no consensus on the level of anaemia that requires investigation there is good evidence to suggest that even individuals with iron deficiency without anaemia are at increased risk of GI malignancy compared with those without iron deficiency, especially if over the age of 50 years [9,18]. Therefore, any level of anaemia should be investigated in patients with iron deficiency, with greater urgency placed on those with a haemoglobin level of less than 9 g/dl.

Diagnosis of IDA relies on interpretation of iron studies. The typical picture seen in IDA is low serum ferritin, low transferrin saturation, and increased total iron binding capacity.

Serum ferritin is by far the best biochemical test as an indicator of iron stores and has replaced the more invasive bone marrow iron stores as the gold standard for diagnosis of IDA [2,24,34–37]. Hypothyroidism and ascorbate deficiency, both of which interfere with ferritin synthesis, are the only two conditions other than iron deficiency capable of lowering serum ferritin [38]. Serum ferritin of less than 15 ng/ml is essentially diagnostic of iron deficiency with a sensitivity of 59% and a specificity of 99% [37]. The diagnostic yield of serum ferritin may be improved by using a cutoff of less than 30 ng/ml, which has a sensitivity and a specificity of 92 and 98%, respectively [39]. Guyatt *et al.* [37] best demonstrated the superiority of serum ferritin over other markers of iron deficiency including serum transferrin, MCV and erythrocyte zinc protoporphyrin in a review of 55 studies.

Because serum ferritin is an acute phase reactant, its usefulness is limited in the presence of infection, malignancies, and acute or chronic inflammation [2,24,35–38]. Elevation of ferritin out of proportion to iron stores is also seen in liver disease, alcoholism and chronic renal failure [35,36]. A higher cutoff for serum ferritin such as less than 60 ng/ml [40] or less than 70 ng/ml [37] may be required to diagnose iron deficiency in this population of patients. Attempts to improve the diagnostic value of serum ferritin by using normograms between ferritin and erythrocyte sedimentation rate or C-reactive protein have shown promise in some studies [41,42] but not in others [43,44].

Serum iron, transferrin, transferrin saturation, and erythrocyte zinc protoporphyrin each have their limitations and are useful in supporting a diagnosis of IDA in situations where serum ferritin is equivocal [35,36]. Interestingly, the combination of serum ferritin and transferrin saturations offers no advantage over serum ferritin alone [36].

Examination of bone marrow aspirate or biopsy was widely regarded as the gold standard for diagnosis of iron deficiency. However, expense, high interobserver variability and invasive nature of the test have made it less favourable. Bone marrow examination should only be considered when the diagnosis of iron deficiency is still uncertain after biochemical investigations [24].

The concentration of serum transferrin receptor (sTfR) is a quantitative measure of total erythropoietic activity, which is elevated in iron deficiency but is not significantly affected by inflammation, infection, age, sex or pregnancy [2]. This makes it a potentially useful test in identifying iron deficiency in patients with inflammatory disease and to discriminate IDA from anaemia of chronic disease although studies have shown conflicting results [39,45–47]. The accuracy of sTfR is limited in the presence of haematological disorders [2,47]. The incorporation of sTfR into the sTfR-ferritin index ($\log_{10}$ serum ferritin) has shown promise as a strong indicator of iron depletion in chronic disease [45]; however, this has failed to be adopted into common clinical practice.

Approach to evaluation

Gastrointestinal evaluation

Occult GI bleeding is the leading cause of IDA in adult males and postmenopausal women. FOBT may be a useful confirmatory test (especially in premenopausal women), but investigation of patents with IDA and no other obvious source of blood loss by endoscopic evaluation of upper and lower GI tracts have become a widely accepted practice [34,48].

Which endoscopic procedure to perform first?

Most patients will be planned and booked for bidirectional endoscopic examination and both procedures should be completed unless a good reason to not proceed is encountered. There is conflicting evidence on the usefulness of site-specific symptoms (upper GI vs. lower GI) in predicting a bleeding lesion at the corresponding site [4–7,10,34,48]. No clear guideline exists on which endoscopic procedure should be performed first and whether

a second endoscopic procedure in the opposite direction is still required if a lesion is found on the first. The evaluation of patients without upper GI symptoms (dysphagia, haematemesis, heartburn, upper abdominal pain) should begin with the colon, especially if they are over the age of 50 years [5,20]. If the initial colonoscopy is negative one should then proceed to upper endoscopy [5,20,48].

Can we stop if pathology is seen after the first endoscopic procedure?

Dual pathology (lesions in both upper and lower GI tracts) is generally uncommon, occurring in 1–9% of patients [4,6,49]. Rockey [5] stipulates that if mass lesions, large ulceration, or severe inflammation is found with either gastroscopy or colonoscopy, further evaluation is unnecessary. The British Society of Gastroenterology recommends that if an upper endoscopy is performed initially, a colonoscopy is not necessary in the presence of gastric cancer or coeliac disease [34]. However, Hopper *et al.* [50] found pathology in 12 out of 98 (12.2%) patients with coeliac disease and IDA who underwent colonoscopy, including three with colonic carcinoma. They have suggested the use of bidirectional endoscopy in patients with coeliac disease and IDA, especially those over the age of 45 years [50]. This highlights that the question of whether a second endoscopic procedure in the opposite direction is necessary to look for dual pathology is not answered conclusively in published literature.

Premenopausal women

IDA in premenopausal women is usually attributed to menstrual and peripartum blood loss and increased iron demands during pregnancy. However, a substantial GI tract lesion is present in 6–30% of premenopausal women with IDA [51–54] with most being erosive lesions found in the upper GI tract from *H. pylori* or NSAID and aspirin use (55–68% of lesions). GI cancers are rare (0–3%) [51–53]. Predictors for having a GI lesion include abdominal symptoms, weight loss of 5 kg or more, a positive FOBT and a haemoglobin level of less than 10 g/dl; MCV < 72 fl were predictive of the presence of a GI lesion [52,54]. The degree of menstrual blood loss was a significant negative predictor for the presence of a GI lesion in one study [52] but was not found to be a useful predictor in another study [51]. On the basis of current available evidence, premenopausal women with GI symptoms, a positive FOBT or a haemoglobin level of less than 10 g/dl should undergo GI evaluation. Age of more than 40 years or a positive family history of GI cancers should also be taken into account when assessing the need for GI evaluation [5,51,53]. All premenopausal women should be screened for coeliac disease, which is present in up to 6% of these individuals [34,52].

Anaemic with normal or low normal ferritin

The prevalence of GI malignancies in anaemic patients without iron deficiency is low with one study demonstrating 0 out of 100 cases (0%) in anaemic patients without iron deficiency compared with 42 out of 271 cases (15%) in patients with IDA [55]. Sawhney *et al.* [56] reported the rates of colonic carcinoma in 55 anaemic individuals with low normal ferritin (50–100 ng/ml) were similar in those with ferritin less than 50 ng/ml (7.2% vs. 7.9%) [56]. The investigators recommended that the serum ferritin limit should be raised from 50 to 100 ng/ml when determining the need for colonoscopy in patients with anaemia. This is not supported by a recent study of 54 males with unexplained anaemia and low normal ferritin (40–100 ng/ml), which found 0 out of 53 (0%) malignancies on colonoscopy and only one out of 47 (2%) malignancies on oesophagogastroduodenoscopy [57]. The study did, however, find significant (malignant and nonmalignant) upper and lower GI lesions in 30 and 6.7% of patients, respectively; suggesting endoscopic evaluation of GI tract of these patients was still worthwhile. Evaluation of the GI tract in patients with ferritin of more than 100 ng/ml (in the absence of an acute phase response) should not be the first line of investigation.

Iron deficiency without anaemia

GI investigation of patients with iron deficiency who are not anaemic is less well studied. Ioannou *et al.* [18] revealed that the risk of GI malignancy in men and premenopausal women with iron deficiency and no anaemia was increased by five times compared with nonanaemic, noniron-deficient individuals. The absolute prevalence is still low at two out of 223 (1%) malignancies; and all GI malignancies were found in patients over the age of 65 years. A recent Korean study of 1518 individuals with iron deficiency (769 had normal haemoglobin), identified similar rates of clinically important lesions in patients with anaemia and without anaemia (24.6 vs. 22.8%, respectively) [9]. Malignant GI lesions were found in 1.3% of iron-deficient patients without anaemia over the age of 50 years compared with only one GI malignancy (< 0.3 %) found in iron-deficient patients, without anaemia, less than 50 years old. These studies support the recommendation that only postmenopausal women and men over the age of 50 years with iron deficiency, who are not anaemic, should undergo GI investigation [34].

Other investigations

Radiographic studies such as barium enema, small bowel series, computed tomography or computed tomography colonography are not entirely reliable for detection of mucosal lesions but may provide an alternative in patients who are unable to undergo endoscopy safely [24].

Obscure bleeding

Obscure gastrointestinal bleeding (OGIB) is defined as persistent or recurrent bleeding from the GI tract after negative evaluations with upper and lower endoscopies. It can be further classified as obscure-overt GI bleeding in patients with clinically evident bleeding (haematemesis, melaena or haematochezia) or obscure-occult GI bleeding, which presents with IDA or a positive FOBT. In patients

with IDA, up to 30–40% have no cause found on upper and lower endoscopies [6,7].

Evaluation of the small bowel is usually the next step as small bowel lesions account for a large proportion of these patients [58]. The development of the wireless capsule endoscopy (CE) has dramatically changed the investigation of OGIB. It is a safe, minimally invasive and effective tool in the evaluation of IDA after negative standard endoscopies. A large systematic review of 227 studies on CE revealed that OGIB was by far the most common indication for referral, comprising 66% of patients [59]. The same review quoted a diagnostic yield of 60.5% with the most common lesions being angiodysplasias (50%), ulcers (26.8%) and neoplastic lesions (8.8%) [59]. In the specific setting of IDA, detection rates vary between 32 and 77% [60].

CE has repeatedly been shown to be superior to push enteroscopy and small bowel radiography in detecting small bowel lesions [58,60–63]. Pooled data from a meta-analysis of 11 studies demonstrated that double balloon enteroscopy (DBE) and CE have similar diagnostic yields of 57% and 60%, respectively, in patients with OGIB [64]. As it is less invasive, CE should be the initial diagnostic test for patients with IDA due to OGIB, unless there is a contraindication. DBE is indicated after a positive CE for biopsy or therapeutic intervention or for patients in whom suspicion of small bowel bleeding is high despite a negative initial CE [64–67]. This approach has been shown to stop bleeding and normalize haemoglobin in more than 75% of patients as well as reduce transfusion and iron requirements [68]. Push enteroscopy is still used for lesions within 50–150 cm of the proximal small bowel [58].

Repeat upper or lower endoscopy

Bleeding lesions within the reach of conventional upper and lower endoscopies are common. These 'missed' lesions are identified in 10–64% of patients with OGIB on push enteroscopy [69–72] and 24–25% of patients on DBE [73,74]. These include Cameron lesions (gastric erosions or ulcerations at the diaphragmatic impression of large hiatus hernias), peptic ulcers, vascular ectasias and watermelon stomach on upper endoscopy and angioectasias on colonoscopy. [24,48,69–72]. An Australian study of 50 patients with OGIB demonstrated that repeat upper and lower endoscopies after initial (negative) endoscopic evaluations detected a missed lesion in only two patients (4%). This approach was less cost-effective than progressing directly onto CE [75]. Patients with OGIB should therefore proceed straight to CE as the next test with a close inspection of the stomach and colon for potential missed lesions. Repeat endoscopic examinations should be considered in patients with ongoing overt bleeding or poor visualization on initial examination [58].

Other investigations

The role of radiographic studies such as small bowel series and enteroclysis in IDA patients has become limited with the advent of CE and DBE. The diagnostic yields for small bowel series and enteroclysis in OGIB are 0–5 [6,76], and 0–20% [7,77], respectively. These investigations are ineffective for detecting mucosal lesions such as angioectasias, which are the most common cause of small bowel bleeding accounting for up to 80% of obscure bleeding cases [5,58]. The use of small bowel series or enteroclysis is therefore not indicated for evaluation of IDA unless there is suspicion of bowel obstruction secondary to malignancy or Crohn's disease preventing the safe passage of a CE [58].

Radionuclide labelled red cell scans and angiography are sensitive for bleeding lesions if the rate is more than 0.1 and 0.5 ml/min, respectively [48]. Angiography also provides the advantage of therapeutic intervention with embolization. The use of these studies is limited to situations where there is rapid bleeding and where other modalities have failed.

Treatment

The treatment of IDA should aim to identify and correct the underlying cause to avoid ongoing blood loss and/or malabsorption. Equal importance should also be placed on starting iron supplementation promptly to replenish stores, relieve symptoms and re-establish effective erythropoiesis.

Oral replacement is first line because it is safe, cheap, convenient and effective in restoring iron balance. Iron tablets should not be taken with food because the phosphates, phytates and tannates found in food impair iron absorption. Ascorbic acid (250–500 mg) taken at the time of iron ingestion may enhance its absorption by providing an acidic environment [78]. Antacids, H_2 blockers and proton pump inhibitors reduce iron absorption; and coingestion should be avoided. Although the recommended dose for treatment of adults with IDA is 100–200 mg of elemental iron per day [2,79], lower doses may be equally as effective while having significantly fewer adverse effects [80,81]. There is neither any evidence to suggest that a particular iron preparation is more effective than another in equivalent doses nor is there consensus on the duration of iron supplementation for IDA. It is reasonable to continue oral iron for 3–6 months after normalization of haemoglobin [34]. Approximately 10–20% of patients experience GI symptoms such as nausea, vomiting and epigastric discomfort after taking oral iron therapy. These effects appear to be dose-dependent and can be avoided by introducing oral iron at a daily low dose after meals before increasing slowly [80]. Enteric-coated iron preparations, although associated with fewer GI side-effects are less well absorbed compared with standard preparations due to release of iron further down the intestinal tract [82]. Infrequently, parenteral iron therapy is required due to intolerance. With appropriate therapy, reticulocytosis occurs within 3–5 days, peaking at 8–10 days and the haemoglobin concentration begins to increase after 1 week [83]. Patients with severe (< 10 g/dl) anaemia often require

Table 2 Nondextran intravenous iron preparations

	Ferric gluconate	Iron sucrose	Ferumoxytol	Ferric polymaltose	Ferric carboxymaltose	Iron isomaltose
Carbohydrate	Gluconate	Sucrose	Polyglucose sorbitol carboxymethylether	Polymaltose	Carboxymaltose	Isomaltose
Maximal approved dose (mg)	125	200	510	2500	15 mg/kg up to 1000 mg (if weight >66 kg)	20 mg/kg
TDI possible	No	No	No	Yes	Yes	Yes
Elemental iron (mg)/ampoule	62.5	100	510	100	100 and 500	100, 500, 1000

TDI, total dose infusion.

parenteral iron as haemoglobin concentrations may take up to 6 weeks to normalize with oral supplementation.

Parenteral iron is indicated in patients with intolerance or noncompliance to oral preparations, inadequate absorption or when a patient's iron losses exceed the maximum amount of iron the GI tract can absorb (e.g. uncontrolled blood loss) [34,35]. Intramuscular iron is not a safer alternative to intravenous iron and is associated with painful injections, permanent skin discolouration and gluteal sarcomas [84]. Its use should therefore be discouraged.

The quicker release of intravenous iron into the circulation for erythropoiesis is offset by the risk of serious adverse reactions including anaphylaxis. Previously popular iron dextran formulations have now been replaced by newer, safer preparations including iron polymaltose, iron sucrose, ferric gluconate, and more recently ferric carboxymaltose, iron isomaltose and ferumoxytol.

A large study of adverse effects on over 30 million doses of parenteral iron showed that absolute rates of life-threatening adverse drug events were 0.6, 0.9, 3.3 and 11.3 per million for iron sucrose, ferric gluconate, lower molecular weight iron dextran and higher molecular weight iron dextran, respectively [85]. Nonlife-threatening adverse reactions (hypotension, diarrhoea, nausea, arthralgias) are also less frequent with ferrous gluconate and iron sucrose preparations compared with iron dextran, however, they become more common when higher doses are administered. For this reason, higher-than-recommended doses of ferrous gluconate (> 125 mg) and iron sucrose (> 200 mg) should be avoided and patients may require repeated infusions to replenish iron stores [86]. In contrast, more rapid administration of large (total dose) infusions can be achieved with iron polymaltose, isomaltose, and ferric carboxymaltose preparations with minimal risk of serious adverse events [84]. Ferumoxytol similarly allows large doses (up to 510 mg of iron) per infusion [86]. A comparison of the newer parenteral iron preparations is shown in Table 2.

In IDA patients with chronic GI bleeding, there is a paucity of literature comparing oral versus intravenous iron as well as studies comparing different intravenous preparations [86]. Research is also needed to guide dosing and frequency of iron infusions in IDA.

Blood transfusions are overused and potentially dangerous in the treatment of IDA [87]. Timely use of iron replacement therapy can eliminate or reduce the need for transfusions [84]. Blood transfusions should therefore be reserved for those with haemodynamic instability or end-organ ischaemia from acute GI bleeding.

Summary

IDA is still an important public health issue in the developed world today. Adult men and postmenopausal women should be evaluated for GI bleeding and malabsorption with gastroscopy and colonoscopy. A small proportion of patients have OGIB requiring CE. Treatment consists of both correcting the underlying cause and prompt iron replacement therapy. Oral iron therapy is preferred unless there are issues with intolerance or absorption. Newer intravenous iron formations are efficacious, safe, and permit rapid administration of large doses of iron replacement.

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Conflicts of interest

There are no conflicts of interest.

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