Guidance for the gastrointestinal evaluation and management of iron deficiency in Sub-Saharan Africa

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Background. Over 30% of the world's population is anaemic, with a significant proportion of these being iron deficient. As iron deficiency (ID) anaemia in men and post-menopausal women is mostly caused by gastrointestinal blood loss or malabsorption, the initial evaluation of a patient with ID anaemia involves referral to a gastroenterologist. The current drive towards patient blood management in sub-Saharan Africa (SSA)prescribes that we regulate not only the use of blood transfusion but also the management of patients in whom the cause of iron loss or inadequate iron absorption is sought. Recommendations have been developed to: (i) aid clinicians in the evaluation of suspected gastrointestinal iron loss and iron malabsorption, and often a combination of these; (*ii*) improve clinical outcomes for patients with gastrointestinal causes of ID; (*iii*) provide current, evidence-based, context-specific recommendations for use in the management of ID; and (*iv*) conserve resources by ensuring rational utilisation of blood and blood products.

Method. Development of the guidance document was facilitated by the Gastroenterology Foundation of Sub-Saharan Africa and the South African Gastroenterology Society. The consensus recommendations are based on a rigorous process involving 21 experts in gastroenterology and haematology in SSA. Following discussion of the scope and purpose of the guidance document among the experts, an initial review of the literature and existing guidelines was undertaken. Thereafter, draft recommendation statements were produced to fulfil the outlined purpose of the guidance document. These were reviewed in a round-table discussion and were subjected to two rounds of anonymised consensus voting by the full committee in an electronic Delphi exercise during 2022 using the online platform, Research Electronic Data Capture. Recommendations were modified by considering feedback from the previous round, and those reaching a consensus of over 80% were incorporated into the final document. Finally, 44 statements in the document were read and approved by all members of the working group.

Conclusion. The recommendations incorporate six areas, namely: general recommendations and practice, *Helicobacter pylori*, coeliac disease, suspected small bowel bleeding, inflammatory bowel disease, and preoperative care. Implementation of the recommendations is aimed at various levels from individual practitioners to healthcare institutions, departments and regional, district, provincial and national platforms. It is intended that the recommendations spur the development of centre-specific guidelines and that they are integrated with the relevant patient blood management protocols. Integration of the recommendations is intended to promote optimal evaluation and management of patients with ID, regardless of the presence of anaemia.

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Executive summary of recommendations and practice statements

This summary of the recommendations provides key practice points for the day-to-day evaluation and management of patients. A more detailed description of the evidence used to make the recommendations follows in the full clinical section of the document. Each recommendation has been given a grade, using the following definitions, set by the Australian National Health and Medical Research Council (NHMRC):

- Grade A – body of evidence can be trusted to guide practice.
- Grade B – body of evidence can be trusted to guide practice in most situations.
- Grade C – body of evidence provides some support for recommendation(s), but care should be taken in its application.
- Grade D – body of evidence is weak, and recommendations must be applied with caution.

General recommendations and practice

1.1.1. Iron deficiency is defined as a serum ferritin level below the lower limit of normal for the relevant population, considering the individual testing parameters of the laboratory processing the sample. In general, we recommend using a serum ferritin level < 30 ng/mL to indicate a diagnosis of iron deficiency *(consensus 100%, statement strength – strong, grade C)*.

1.1.2. Gastrointestinal investigations should be considered in all patients with iron deficiency, regardless of the severity of deficiency or status of anaemia. The evaluation of iron deficiency may facilitate the early detection of gastrointestinal malignancies *(consensus 81.3%, statement strength – strong, grade C)*.

1.1.3. Before undertaking invasive gastrointestinal investigations, we recommend screening for haematuria and other potential sources of extra-intestinal blood loss in patients with iron deficiency *(consensus 82.4%, statement strength – strong, grade C)*.

1.1.4. For cases in which non-gastrointestinal causes of iron deficiency have been excluded, the decision to perform initial sequential or bidirectional endoscopy should be made based on the clinical scenario, assessment by the clinician, and input from the patient *(consensus 100%, statement strength – strong, grade C)*.

1.1.5. In pre-menopausal women with iron deficiency, in whom dietary causes and menorrhagia have been excluded, upper endoscopy and the administration of iron replacement therapy are recommended. If upper endoscopy findings are normal and the response to iron replacement therapy is sub-optimal, and/or there is a significant history of colorectal malignancy, we recommend lower endoscopy *(consensus 93.8%, statement strength – strong, grade C)*.

1.1.6. In patients with iron deficiency, computer tomography colonography, where available, is an alternative if colonoscopy is contra-indicated *(consensus 82.4%, statement strength – strong, grade B)*.

1.1.7. Sigmoidoscopy may provide a diagnosis in certain circumstances, e.g. rectal bleeding from haemorrhoidal disease or distal malignancy; however, a complete evaluation of the lower gastrointestinal tract should be performed *(consensus 100%, statement strength – strong, grade B)*.

1.1.8. Digital rectal examination as part of the initial evaluation is recommended. Suspicious findings during digital rectal examination may be used to motivate timeous endoscopy where access to colonoscopy services is limited *(consensus 100%, statement strength – strong, grade D)*.

1.1.9. Faecal occult blood testing, a screening test for colorectal neoplasia, is seldom of benefit in the investigation of iron deficiency *(consensus 82.4%, statement strength – strong, grade C)*.

1.1.10. In patients with iron deficiency, intolerance or non-responsiveness to oral iron is common. We recommend the administration of intravenous iron in these cases *(consensus 94.1%, statement strength – strong, grade C)*.

1.1.11. Patients undergoing gastrectomy or bariatric surgery should be monitored for iron deficiency and treated accordingly. Treating patients with oral iron after gastrectomy is not recommended. The administration of intravenous iron is preferable in these cases *(consensus 100%, statement strength – strong, grade B)*.

Helicobacter pylori

1.2.1. In patients with unexplained iron deficiency, we recommend testing for *H. pylori* during upper gastrointestinal investigations (e.g., using a rapid urease test or histopathology) *(consensus 100%, statement strength – strong, grade C)*.

1.2.2. We recommend performing non-invasive tests for *H. pylori*, e.g. urea breath test or stool antigen test in patients with unexplained iron deficiency and normal endoscopy findings in whom prior testing for *H. pylori* was not performed *(consensus 88.3%, statement strength – strong, grade C)*.

1.2.3. We recommend the administration of eradication therapy in all patients with *H. pylori* infection and iron deficiency. Iron replacement therapy should be introduced following the completion of eradication to reduce non-compliance owing to gastrointestinal side-effects *(consensus 94.1%, statement strength – strong, grade C)*.

1.2.4. We recommend confirming the eradication of *H. pylori* infection using a non-invasive test, e.g. stool antigen test *(consensus 82.4%, statement strength – strong, grade C)*.

Coeliac disease

1.3.1. We recommend performing evaluations for coeliac disease (CD) in all patients with unexplained and/or recurrent ID. Initial coeliac serology followed by small bowel biopsies in sero-positive patients is recommended over routine small bowel biopsies *(consensus 93.8%, statement strength – strong, grade C)*.

1.3.2. Patients with ID and confirmed CD should be managed with a strict gluten-free diet and iron replacement therapy *(consensus 100%, statement strength – strong, grade B)*.

1.3.3. The presence of CD should not preclude further investigations of ID in males, post-menopausal females, and patients with a positive family history of gastrointestinal malignancy *(consensus 100%, statement strength – strong, grade B)*.

Suspected small bowel bleeding

1.4.1. In patients with normal upper and lower endoscopy, an initial trial of iron replacement therapy with close follow-up is recommended over the routine use of capsule endoscopy. Capsule endoscopy is recommended if the ID proves refractory *(consensus 100%, statement strength – strong, grade C)*.

1.4.2. During the evaluation of suspected small bowel bleeding, re-look upper and lower endoscopy by an experienced endoscopist is recommended, especially if the initial endoscopies were of inadequate quality. If further investigations are required, capsule endoscopy followed by directed small bowel endoscopy is recommended *(consensus 100%, statement strength – strong, grade C)*.

1.4.3. Small bowel investigation using capsule endoscopy should be considered to identify an obscure cause of ID in patients with normal upper and lower endoscopy, or if symptoms suggest small bowel disease *(consensus 94.1%, statement strength – strong, grade C)*.

1.4.4. If capsule endoscopy is unavailable, computed tomography or magnetic resonance enterography is a reasonable alternative for investigating cases of suspected small bowel bleeding *(consensus 94.1%, statement strength – strong, grade C).*

1.4.5. In cases of active, unexplained bleeding, preoperative red cell scintigraphy or computer tomographic angiography and intraoperative enteroscopy through a mid-small bowel enterotomy are recommended, especially in patients where the cause of active bleeding remains obscure *(consensus 81.3%, statement strength – strong, grade C).*

1.4.6. The administration of intravenous iron therapy with close follow-up is strongly recommended for patients with suspected small bowel bleeding of an unknown cause despite active investigations and in patients with ID which is unresponsive to oral iron *(consensus 100%, statement strength – strong, grade C).*

Inflammatory bowel disease

1.5.1. All patients with inflammatory bowel disease should be assessed for the presence of ID and anaemia at the initial diagnosis and should undergo long-term serial monitoring *(consensus 100%, statement strength – strong, grade B).*

1.5.2. Laboratory screening for ID in patients with inflammatory bowel disease should comprise haemoglobin, serum ferritin, and transferrin saturation measurements. In addition, and if available, the measurements of soluble transferrin receptor, reticulocyte haemoglobin content, or hypochromic red cell percentage may be useful in the diagnosis of ID *(consensus 100%, statement strength – strong, grade B).*

1.5.3. In the presence of active inflammatory bowel disease, a normal serum ferritin level does not exclude ID. Transferrin saturation and C-reactive protein should also be measured *(consensus 100%, statement strength – strong, grade B).*

1.5.4. In patients with inflammatory bowel disease and ID, the degree of active inflammation should be determined using objective parameters such as C-reactive protein and faecal calprotectin measurements, endoscopy and/or cross-sectional imaging *(consensus 100%, statement strength – strong, grade C).*

1.5.5. For patients with inflammatory bowel disease and ID who are in remission, measurements of serum ferritin and transferrin saturation levels should be performed routinely, every six to 12 months. In outpatients with active disease, such measurements should be performed at least every three months *(consensus 100%, statement strength – strong, grade C).*

1.5.6. In the absence of clinical, biochemical or endoscopic evidence of inflammation, ID is considered likely if the serum ferritin level is <30 ng/mL. However, in the presence of inflammation, a serum ferritin level of up to 100 ng/mL is consistent with ID and is therefore the appropriate upper level used to diagnose ID in patients with active inflammatory bowel disease. Further, iron stores may still be inadequate at higher serum ferritin levels (even up to 400 ng/mL) if the transferrin saturation level is low *(consensus 100%, statement strength – strong, grade C).*

1.5.7. The therapeutic goal for ID in patients with inflammatory bowel disease is to normalise haemoglobin, serum ferritin, and transferrin saturation levels, replenish iron stores (serum ferritin >100 ng/mL), avoid the need for blood transfusions, and improve the quality of life *(consensus 100%, statement strength – strong, grade C).*

1.5.8. In cases of ID in which the disease is quiescent and Hb is >10 g/dL, the administration of oral iron should be considered as first-line therapy, but only once tolerance to oral iron is established *(consensus 94.1%, statement strength – strong, grade B).*

1.5.9. Patients with ID and active inflammatory bowel disease should ideally be treated with intravenous formulations if the haemoglobin level is <10 g/dL, if there is intolerance or an inadequate response to oral iron, or in the presence of significant inflammation *(consensus 88.3%, statement strength – strong, grade C).*

1.5.10. If considered appropriate, no more than 100 mg of elemental iron per day is recommended in patients with inflammatory bowel disease, and the response to oral iron should be assessed four to eight weeks after the initiation of iron replacement therapy *(consensus 88.2%, statement strength – strong, grade C).*

1.5.11. Following oral iron replacement therapy, the haemoglobin level should increase by at least 2 g/dL from baseline. If this target is not reached within four to eight weeks, intravenous iron replacement therapy should be considered. Thereafter, the haemoglobin level should be measured every four weeks until the anaemia has resolved *(consensus 88.2%, statement strength – strong, grade C).*

1.5.12. Following an intravenous infusion of iron replacement therapy, serum measurements of iron stores should not be repeated for at least four weeks as intravenous iron might lead to falsely raised serum ferritin values in that period. We recommend that intravenous iron replacement therapy be repeated once the serum ferritin falls below 100 ng/mL or when the haemoglobin falls below 12 g/dL and 13 g/dL in women and men, respectively *(consensus 88.2%, statement strength – strong, grade C).*

1.5.13. Following the successful treatment of ID in patients with inflammatory bowel disease, iron levels should be monitored every three months using a combination of haemoglobin, serum ferritin, transferrin saturation, and C-reactive protein testing. Six- to 12-monthly evaluations may be satisfactory in treated and stable patients with inflammatory bowel disease *(consensus 94.1%, statement strength – strong, grade C).*

Preoperative care

1.6.1. Preoperative ID should be investigated using a full blood count, serum ferritin, transferrin saturation, and C-reactive protein before all major surgical procedures and especially in those expected to result in an intraoperative blood loss greater than 400 mL *(consensus 88.2%, statement strength – strong, grade C).*

1.6.2. For patients with identified preoperative ID, elective surgery should be postponed until the haemoglobin has been optimised *(consensus 94.1%, statement strength – strong, grade B).*

1.6.3. We recommend a preoperative haemoglobin target of 13 g/dL for non-urgent surgery in male and female patients *(consensus 87.6%, statement strength – strong, grade C).*

1.6.4. We recommend that preoperative patients with ID without evidence of inflammation and in whom surgery is scheduled for more than eight weeks following the diagnosis, should initially be treated with oral iron replacement therapy *(consensus 94.1%, statement strength – strong, grade D).*

1.6.5. Preoperative patients with ID undergoing oral iron replacement therapy should have their haemoglobin and serum ferritin levels reviewed four weeks after treatment initiation for assessment of response, further workup, and change to intravenous iron where necessary *(consensus 94.1%, statement strength – strong, grade C).*

1.6.6. In the preoperative period, intravenous iron is safe and effective for the treatment of ID with or without inflammation and can be administered in an outpatient setting *(consensus 100%, statement strength – strong, grade B).*

1.6.7. We recommend the use of intravenous iron in preoperative

patients with ID, in whom surgery is scheduled for less than eight weeks after the diagnosis, and in those who are nonresponsive or intolerant to oral iron therapy *(consensus 94.1%, statement strength – strong, grade B).*

Background

Over 30% of the world's population is anaemic, with a significant proportion of these being iron deficient.[1,2] The World Health Organization defines anaemia as a condition in which the number of red blood cells or their oxygen-carrying capacity is insufficient to meet their physiological needs, varied by sex, altitude, smoking and pregnancy status. As iron deficiency anaemia (IDA) in men and post-menopausal women is mostly caused by gastrointestinal (GI) blood loss or malabsorption,[3] the initial evaluation of a patient with IDA involves a referral to the gastroenterologist.

The current drive towards patient blood management (PBM) in Sub-Saharan Africa (SSA) prescribes that we regulate not only the use of blood transfusion in this setting but also the evaluation and care of patients in whom the cause of iron loss or inadequate iron absorption is sought. PBM is an evidence-based bundle of care that aims to optimise patient outcomes by managing and preserving patients' blood. It focuses on the detection, identifying and managing the underlying causes, and the treatment of anaemia. Once identified, the treatment of the underlying cause usually cures the anaemia, and, importantly, even where the cause remains elusive, the outcome of those patients who respond satisfactorily to iron replacement is good.

There are several challenges to patient blood management in SSA, making the development and implementation of the recommendations essential and urgent. These challenges most notably include a high incidence of anaemia, a frequent shortage of blood products, a small donor population, and healthcare systems under financial strain. As a further challenge, there is a mixture of low-, middle- and high-income healthcare structures within SSA, yet the same not-for-profit non-governmental organisations provide blood products to both private and public sectors. In all settings, particularly those with this disparity, the rational and equitable use of blood products is important to ensure the best care for as many critically ill patients as possible. The recommendations focus on the broader principles of PBM in the context of GI causes of ID.

Scope and purpose

This guidance document is provided as an informational resource, intended to assist medical professionals, particularly gastroenterologists in clinical decision-making, in evaluating and managing a patient with ID of a suspected gastroenterological origin. The recommendations focus on providing practical answers to key patient-centered questions and have been based on the best available evidence and expert consensus at the time of publication. The unique requirements of the SSA context have been considered and the guidance document is therefore intended for use in this setting. The recommendations are intended for use in adult patients (i.e., greater than or equal to 18 years of age); however, practitioners may choose to apply them to patients deemed physiologically to be adults and are not intended for use in the obstetric setting. The recommendations may also prove useful for hospital administrators in creating institutional PBM guidelines.

The specific objectives of the guidance document are:

- to aid clinicians in the evaluation of GI iron loss, iron malabsorption, and often, as in the setting of inflammatory bowel disease (IBD), a combination of these
- to improve clinical outcomes for patients with GI causes of ID
- to provide current, evidence-based, context-specific blood management recommendations to be used in the management of ID in SSA
- to conserve resources in SSA by ensuring rational utilisation of blood and blood products.

Guidance development

The development of the guidance document was facilitated by the Gastroenterology Foundation of Sub-Saharan Africa (GFSSA) and the South African Gastroenterology Society (SAGES). While these bodies are supported by various institutions including pharmaceutical companies, no company has been involved in this process. Every effort has been made to ensure that all conflicts of interest, including specific financial interests and relationships, are managed appropriately, and disclosed. The development of the recommendations involved a multi-step approach by the guidance working group.

4.1. Drafting consensus statements

Following a discussion of the scope and purpose of the recommendations, a formal literature search was undertaken by the primary study authors with all subcategories of the term 'iron deficiency' and 'iron deficiency anaemia' using PubMed (pubmed.ncbi.nlm.nih.gov). Considering this literature search, draft statements were produced to fulfil the outlined purpose of the guidance. Additional statements were added, based on local clinical experience. All statements were compiled into sections for review by the guideline working group.

4.2. Guidance working group

Experts in the fields of gastroenterology and haematology were invited by the primary authors to participate in the process. A round-table discussion was then held in Cape Town with representation from numerous major centres across SSA, various specialities, and a mix of public and private sectors. This guideline working group consisted of 21 members who reviewed the draft statements to remove any ambiguity and ensure clarity. The next steps of the process involving the e-Delphi process and Agree II instrument were then discussed.[4,5]

For the round-table discussion, specific input on the statements was sought from other nursing staff, patients and a representative from the local blood service, but all opted out of the process owing to the intricate and technical nature of the subject matter. While absence of lay persons may be viewed as a limitation, the focus of the recommendations remained on engaging experts, practitioners and individuals involved in the evaluation of ID, in guiding them within the field toward best practice and informed decision-making.

4.3. Electronic Delphi process

An e-Delphi process was conducted using the draft statements. The statements were subject to two rounds of anonymised consensus voting by the full committee in an e-Delphi exercise during 2022 using the online platform, REDCap (redcap.ufs.ac.za). The threshold for consensus was set at 80%. Results were collated, and where consensus was not reached, the statements were selected for further review and research. Statements were then redrafted in line with the findings and suggestions made by the e-Delphi respondents and resubmitted for voting.

4.4. Formulation of the consensus statements/ recommendations

The results of the two e-Delphi rounds were collated to form the backbone of the current guidance document. Each recommendation is derived directly from the responses to the statements made by the guideline working group. Consensus was achieved for all but one recommendation, and the recommendations thus represent a synthesis of the best available current research evidence and the practical experience of SSA gastroenterology and haematology clinicians. The recommendation strength (strong, weak) was based on a range of factors including (as appropriate) the degree of consensus, the perceived risk/benefit balance, and expert opinion.

4.5. In-depth literature review

A further in-depth literature review was then performed by the primary authors to identify existing guidelines and research to consolidate the evidence base surrounding each recommendation for presentation in the guidance document. A narrative review format was followed using the research to grade the evidence for each statement according to the Australian NHMRC definitions and to provide the evidence for each statement in the full guidance document.

4.6. Formulation of the guidance document

The guidance document draft was prepared by the primary authors and sent to other members of the working group for review and comments, after which the draft was modified and sent back to the group for a second review process. The final version was then adopted after this second review process. The recommendations incorporate six areas, namely: general recommendations and practice, *H. pylori* (HP), CD, suspected small bowel bleeding (SSBB), IBD and preoperative care. Information regarding the e-Delphi consensus, recommendation strength and NHMRC grading is summarised for each statement in the executive summary.

Anaemia

The haemoglobin (Hb) cut-off value for anaemia in men is 13g/dL and, for non-pregnant women, 12g/dL.[1] There is little consensus as to the level of anaemia that warrants investigation.[2]

Iron deficiency

Here, ID is defined as a serum ferritin (SF) level below the lower limit of normal for the relevant population, considering the individual testing parameters of the laboratory processing the sample. In general, we recommend using an SF level <30 ng/mL to indicate a diagnosis of ID. Other serum markers of ID include low transferrin saturation (TfS) with saturations less than 20% being indicative of ID, low serum iron, raised total iron-binding capacity, raised red cell zinc protoporphyrin, increased soluble transferrin receptor (sTfR), low reticulocyte Hb (Retic-Hb) and a raised percentage of hypochromic red cells.[4,5]

Automated cell counters provide measurements of changes in red cells that accompany ID including reduced mean corpuscular Hb (MCH) (hypochromia) and reduced mean corpuscular volume (MCV) (microcytosis).[6] MCH is probably more reliable as a marker of ID as it is less dependent on the counter used and a reduction in MCH is seen in both absolute and functional ID.[4] However, both microcytosis and hypochromia lose sensitivity for ID in the presence of chronic disease, thalassaemia or vitamin B12/folate deficiency.[7] In addition, the specificity of MCV and MCH for ID is low, as microcytosis and hypochromia also occur in many haemoglobinopathies, in sideroblastic anaemia, and in some cases in anaemia of chronic disease.[4]

While SF is the most specific test for ID in the absence of inflammation,[8] as an acute-phase protein, apparently normal levels may occur with ID in the context of an inflammatory disease process.[6] Given that chronic inflammatory conditions are common and that SF values may therefore be difficult to interpret, it is important to use additional clinical and laboratory information when considering whether further GI investigations are warranted. Clinical features, e.g. GI symptoms, inflammatory markers (C-reactive protein), TfS, and red cell hypochromia can all be useful in this setting. An SF level of up to 100 ng/mL in the setting of inflammation is consistent with ID and is therefore the appropriate upper level used to diagnose ID in patients with active inflammation. Further, iron stores may still be inadequate at higher SF levels (even up to 400 ng/mL) if the TfS is low. The sTfR concentration is also a good marker of ID in otherwise healthy subjects,[5] but it can also be raised where there is increased erythropoietic drive such as with haemolytic anaemia and thalassaemia.[8]

Iron deficiency anaemia

The diagnostic criteria for anaemia in IDA vary between published studies.[9-14].

Clinical picture and initial diagnosis

IDA is a common clinical problem with a degree of case homogeneity.[15] Clinical assessment of a subject with IDA may reveal manifestations of anaemia, such as pallor, breathlessness, fatigue and even heart failure.[4] Manifestations more specific for ID may be present, such as angular stomatitis, glossitis, koilonychia, restless leg syndrome, pagophagia (pica for ice), geophagia (pica for soil), blue sclerae or dysphagia owing to oesophageal webbing.[4] History may reveal altered behaviour and/or poor scholastic performance. A personal or family history of GI disease may indicate the cause of IDA. A family history of true iron-refractory IDA is rare but, if given, may suggest a genetic disturbance of the pathway controlling iron absorption. Even if present, GI symptoms are not a reliable guide to the presence, nature or location of underlying GI pathology.[16]

There are many potential contributors to ID. Particular risk factors that should be sought include chronic overt blood loss (e.g. menstruation, nosebleeds), blood donation, long-term non-steroidal anti-inflammatory drug (NSAID) use, inadequate dietary intake, and previous resection or bypass surgery of the GI tract.[4] More recently it has been recognised that long-term proton pump inhibitor therapy may contribute to the risk of ID and that IDA is common in endurance athletes, possibly owing to high hepcidin levels.[17] ID is, however, commonly multifactorial, and so the presence of one or more of these risk factors should not necessarily be a deterrent to further GI investigation, particularly in older age groups.[4]

Physical examination in ID is often unremarkable, but may sometimes provide additional indicators such as splenomegaly, and in rare cases may give a diagnosis, for example, in hereditary haemorrhagic telangiectasia. Digital rectal examination (DRE) as part of the initial evaluation is recommended. Suspicious findings during DRE may be used to motivate timeous endoscopy where access to colonoscopy services is limited.

Gastrointestinal investigation

GI investigation should be considered in all patients with ID, regardless of the severity of deficiency or status of anaemia. The evaluation of ID may facilitate the early detection of GI malignancies. However, before undertaking invasive GI investigations, we recommend screening for haematuria[18] and other potential sources of extra-intestinal blood loss in patients with ID.[3]

Standard practice is to examine the upper and lower GI tracts at gastroscopy and colonoscopy, respectively.[4,12,19] For cases in which non-gastrointestinal causes of ID have been excluded, the decision to perform initial sequential or bidirectional endoscopy should be made based on the clinical scenario, assessment by the clinician, and input from the patient. It is often more efficient to perform bidirectional endoscopy as the patient is already prepared and the decision to proceed to colonoscopy is simplified if there are abnormalities of uncertain relevance to ID in the upper GI tract.[4,12,19] However, in pre-menopausal women with ID, in whom dietary causes and menorrhagia have been excluded, upper endoscopy and the administration of iron replacement therapy (IRT) are recommended, rather than immediate bidirectional endoscopy. If upper endoscopy findings are normal and the response to IRT is sub-optimal, and/or there is a significant history of colorectal malignancy, we recommend conducting lower endoscopy.[4]

In patients with ID, computer tomographic (CT) colonography, where available, is an alternative if colonoscopy is contraindicated.[3,20,21] It may also be preferable in certain clinical situations, such as in the presence of major comorbidities.[4] The advantage of CT colonography is that it is less invasive, does not require sedation, and provides limited imaging of the other viscera. The disadvantage is that it does not identify more subtle mucosal pathology such as vascular malformations, flat lesions, and small polyps <5 mm in diameter. Further, there may be circumstances where a colonoscopy is subsequently required to obtain histology or remove a lesion.

Sigmoidoscopy may provide a diagnosis in certain circumstances, e.g. rectal bleeding from haemorrhoidal disease or distal malignancy. However, a complete evaluation of the lower GI tract should be performed. Faecal occult blood testing (FOBT), a screening test for colorectal neoplasia, is seldom of benefit in the investigation of ID.[3]

Who to investigate?

Investigation of ID and IDA potentially involves a considerable workload and cost with a relatively low yield, and so there is a strong case, particularly in the setting of SSA, for targeting valuable investigational resources. Cancer is the most serious pathology underlying IDA, but even when only investigating males and post-menopausal females, cancer is found in just 8 - 10% of cases.[16]

8.1. Malabsorptive conditions

Most IDA is due to poor dietary intake. Dietary iron is absorbed in the duodenum and proximal jejunum. Plasma iron homeostasis is regulated by the pH; the low pH of gastric acid facilitates conversion of the insoluble ferric (Fe^{3+}) to absorbable ferrous (Fe^{2+}) ions. For this reason, proton-pump inhibitors may impede iron absorption.[22] Iron absorption can also be facilitated or inhibited by certain foods or compounds; for instance, foods containing phytates, polyphenols and calcium inhibit absorption. Additionally, diseases of the stomach and duodenum can affect iron absorption; these include peptic ulcer disease, Crohn's disease, CD, tropical sprue, familial adenomatous polyposis, intestinal tuberculosis, cystic fibrosis, *H. pylori* infection[23] and post-gastroduodenal surgery.

The most frequent cause of anaemia post gastrectomy is the combination of iron and vitamin B12 deficiency.[24] Obesity reduction procedures, including gastric bypass, laparoscopic adjustable gastric banding, vertical banded gastroplasty, biliopancreatic diversion, and biliopancreatic diversion with duodenal switch, have all been associated with mineral deficiencies, including iron, to varying degrees, depending on the extent of duodenal preservation.[25] The mechanism for IDA in these instances is impairment of iron absorption owing to operative bypass of the stomach or duodenum, rapid intestinal transit, and reduction in gastric acid. It is therefore recommended that patients undergoing gastrectomy or bariatric surgery are monitored for ID and treated accordingly. Treating patients with oral iron after gastrectomy is not recommended. The administration of IV iron is preferable in these cases.[25]

8.2. *H. pylori*

The prevalence of *H. pylori* (HP) in Africa is as high as 70.1%.[26] Currently, available data support the association between HP and ID or IDA.[27] Compared with HP-negative individuals, those with asymptomatic infection had a three-times increased risk of IDA, and a 1.4-times increased risk of ID.[28] Data from eight randomised control trials showed greater improvement in Hb with HP eradication and iron therapy combined, compared with iron replacement alone.[23] The mechanism of this is poorly understood and, given the high prevalence of HP worldwide, it is unclear why a small proportion of these patients have IDA.

In patients with unexplained ID, we recommend testing for HP during upper GI investigations (e.g. using a rapid urease test or histopathology). We recommend performing non-invasive tests for HP, e.g. urea breath test (UBT) or stool antigen test (SAT) in patients with unexplained ID and normal endoscopy findings in whom prior testing for HP was not performed.

Eradication therapy should be administered in all patients with HP infection and ID. IRT should be introduced following the completion of eradication to reduce non-compliance owing to GI side-effects. Importantly, we recommend confirming the eradication of HP infection using a non-invasive test, e.g. SAT.

8.3. Coeliac disease

CD is the most prototypical malabsorptive cause for IDA. Anaemia is reported as the sole or most frequent extra-intestinal manifestation of CD,[29-31] with the most common type being IDA. ID occurs in up to 46% of patients with subclinical/undiagnosed CD.[30] CD is frequently diagnosed in patients referred for evaluation of IDA, being reported in 1.8 - 14.6% of patients.[32] The main mechanism of ID in CD is inflammation,[8] rather than blood loss. The evidence for the former is that anaemia of chronic disease is also described in CD,[33,34] and a gluten-free diet over 12 months results in the improvement of IDA.[34] Women with IDA are twice as likely as males to have CD;[35] in fact, studies report that 73 - 100% of IDA patients diagnosed with CD are pre-menopausal women.[32] This is explained by the combination of menstrual blood loss and chronic inflammation[8] owing to the CD.

We recommend performing evaluations for CD in all patients with unexplained and/or recurrent ID. While duodenal biopsy histology remains the gold standard for exclusion or confirmation of the diagnosis, initial coeliac serology followed by small bowel biopsies in seropositive patients is recommended over routine small bowel biopsies.[19, 36-38] A prospective study of 2 000 referrals for a gastroscopy (all indications including anaemia, mean age 56 years) with parallel serology and histology yielded both a sensitivity and

a specificity of anti-tissue transglutaminase (tTG) for CD of 90.9%, with a negative predictive value of 99.6%.[35] Patients with ID and confirmed CD should be managed with a strict gluten-free diet and iron supplementation.[30,31]

The presence of CD should not preclude further investigations of ID in males, post-menopausal females, and patients with a positive family history of GI malignancy. In an older subject with ID, the sensitivity of serology for CD is lower, while the probability of other pathology and, in particular, GI malignancy is much higher, and dual pathology is also more common.[38] Therefore, in older subjects, additional investigations such as bidirectional endoscopy should be strongly considered.

8.4. Suspected small bowel bleeding

In patients with normal upper and lower endoscopy, an initial trial of iron supplementation therapy with close follow-up is recommended over the routine use of capsule endoscopy. If there are concerns about the date or quality of the initial endoscopies, re-look upper and lower endoscopies by an experienced endoscopist is recommended.

However, if available, capsule endoscopy is recommended if symptoms suggest small bowel disease or if the ID is refractory in the presence of normal upper and lower endoscopy. The diagnostic yield of small bowel examination by capsule endoscopy is high in recurrent ID unexplained by adequate visualisation of the upper and lower GI tract.

Common findings on capsule endoscopy include angioectasia, Crohn's disease, and NSAID-related enteropathy.[35,36,39,40] It is also worth noting that capsule endoscopy with longer transit times is associated with a higher diagnostic yield.[41,42] The possibility of missed pathology should be considered with capsule endoscopy when the transit time is rapid.

If capsule endoscopy is unavailable, computed tomographic (CT) or magnetic resonance (MR) enterography is a reasonable alternative for investigating cases of suspected small bowel bleeding. Capsule endoscopy is more reliable for identifying angiodysplasia and inflammation, while enterography is probably more reliable for detecting malignancy, although this is a tentative conclusion owing to small numbers.[43] As most small bowel lesions underlying ID are subtle vascular or inflammatory abnormalities, capsule endoscopy has been the preferred option, with enterography being a complementary investigation.[44,45] However, enterography does have a role in delineating small bowel tumours, and the combination of arterial venous and phases is helpful in characterising vascular small bowel tumours and detecting metastases. In addition, enterography may reveal evidence of other neoplasia underlying ID, such as lymphoma or tumours of the renal tract. In line with this approach, meta-analyses have concluded that enterography and capsule endoscopy are best considered complementary investigations.[46,47]

In cases of active, unexplained bleeding, preoperative red cell scintigraphy or CT angiography and intraoperative enteroscopy through a mid-small bowel enterotomy are recommended, especially in patients where the cause of active bleeding remains obscure.

The administration of IV iron therapy with close follow-up is strongly recommended for patients with SSBB of an unknown cause despite active investigations and in patients with ID which is unresponsive to oral iron. IV iron supplementation can be a useful therapeutic test, suggesting iron loss over malabsorptive cause in the event of poor response.

In many smaller or rural facilities in SSA capsule endoscopy, enterography, CT angiography or the option for intraoperative enteroscopy will not be available, and practitioners are recommended to refer patients to a centre with these facilities where possible. If this is not an option, relook upper and lower endoscopies can be considered.

8.5. Inflammatory bowel disease

Anaemia is one of the most common complications of IBD and is the most prevalent extra-intestinal manifestation of both Crohn's disease and ulcerative colitis.[48] In most cases, IBD-associated anaemia is due to a combination of ID and anaemia of chronic disease.[48] Other causes of anaemia in this setting are vitamin B12 deficiency, folate deficiency, and haemolysis or bone marrow suppression secondary to IBD medications.[49]

ID in IBD is usually multifactorial and occurs through blood loss from ulcerated mucosal surfaces but may also be due to decreased dietary intake or malabsorption.[50] The impact of anaemia on patients with IBD is substantial. It is frequently associated with a reduced quality of life and an inability to work.[50] As such, an essential component of the management of patients with IBD is the prevention of anaemia and the maintenance of iron and vitamin stores.

All patients with IBD should be assessed for the presence of ID and anaemia at the initial diagnosis and should undergo long-term serial monitoring.[48] Laboratory screening for ID in patients with IBD should comprise Hb, SF and TfS measurements. In addition, and if available, the measurements of sTfR,[5] reticulocyte Hb content or hypochromic red cell percentage may be useful in the diagnosis of ID.

A third of patients with active IBD are estimated to have ID. In the presence of active IBD, a normal SF level does not exclude ID and TfS, and CRP should also be measured.[51] In patients with IBD and ID, the degree of active inflammation should be determined using objective parameters such as CRP[8] and faecal calprotectin measurements, endoscopy and/or cross-sectional imaging. In the absence of clinical, biochemical or endoscopic evidence of inflammation, ID is considered likely if the SF level is <30 ng/mL. In the presence of inflammation, an SF level of up to 100 ng/mL is consistent with ID,[50] and is therefore the appropriate upper level used to diagnose ID in patients with active IBD. Further, iron stores may still be inadequate at higher SF levels (even up to 400 ng/mL) if the TfS is low. The therapeutic goal for ID in patients with IBD is to normalise Hb, SF, and TfS levels, replenish iron stores (SF > 100 ng/mL), avoid the need for blood transfusions, and improve the quality of life.

In cases of ID in which the disease is quiescent and Hb is >10 g/dL, the administration of oral iron should be considered as first-line therapy, but only once tolerance to oral iron is established. Patients with ID and active IBD should avoid oral iron and ideally be treated with IV formulations if the Hb level is <10 g/dL, as the absorption of oral iron may be impaired by the systemic inflammatory process,[52,53] as well as by small bowel involvement and/or previous surgery.

If considered appropriate, no more than 100 mg of elemental iron per day is recommended in patients with IBD,[48,54] and the response to oral iron should be assessed four to eight weeks after the initiation of IRT. The absorption of oral iron may be impaired in IBD[55,56] so regular review of the response to oral iron therapy is essential. Following oral iron supplementation, the Hb level should increase by at least 2 g/dL from baseline. If this target is not reached within four to eight weeks, IV iron therapy should be considered. Thereafter, the Hb level should be measured every four weeks until the anaemia has resolved.[48,57,58]

Following an IV infusion of iron therapy, serum measurements of iron stores should not be repeated for at least four weeks as IV iron might lead to falsely raised SF values in that period. We recommend that IV iron therapy be repeated once SF falls below 100 ng/mL or when Hb falls below 12 g/dL and 13 g/dL in men and women, respectively.[59] Recurrent IDA may indicate persistent intestinal inflammatory activity even in the face of clinical remission and normal inflammatory biomarkers.[48] Following the successful treatment of ID in patients with IBD, iron levels should be monitored every three months using a combination of Hb, SF, TfS and CRP testing.[48] Six- to 12-monthly evaluations may be satisfactory in treated and stable patients with IBD.

8.6. Preoperative care

Preoperative ID should be investigated using a full blood count, SF, TfS and CRP before all major surgical procedures and especially in those expected to result in an intraoperative blood loss greater than 400 mL. Although initially >500 mL was used as a trigger by consensus guidelines, subsequent data has shown worse oncological outcomes with blood loss >200 mL.[60] For patients with identified preoperative ID, elective GI surgery should be postponed until the Hb has been optimised. We recommend a preoperative Hb target of 13 g/dL for non-urgent surgery in male and female patients.[60]

Preoperative patients with ID without evidence of inflammation and in whom surgery is scheduled for more than eight weeks following the diagnosis should initially be treated with oral iron using a low-dose, alternate-day regimen if ferrous iron preparations are used. Sucrosomial or ferric iron (e.g. iron polymaltose) preparations are used once daily. These patients should then have their SF and Hb levels reviewed four weeks after treatment initiation to assess for an adequate response, further evaluation, and change to IV iron where necessary.

In the preoperative period, IV iron is safe and effective for the treatment of ID with or without inflammation and can be administered in an outpatient setting. We recommend the use of IV iron in preoperative patients with ID and inflammation, in whom surgery is scheduled for less than eight weeks after the diagnosis, and in those who are nonresponsive or intolerant to oral iron therapy.

Iron replacement therapy

The treatment of IDA aims to restore normal circulating Hb levels, replenish body iron stores, improve quality of life, and improve physiological function. Successful IRT should achieve all these outcomes.[54]

9.1. Oral iron

It is usual to start treatment for IDA as soon as the diagnosis has been confirmed by laboratory investigation so that the treatment and investigation of IDA proceed in parallel. There is usually a beneficial rise in Hb within two weeks of commencing oral IRT.[61] Oral iron preparations often stain the stools and may cause constipation, so it is usual practice to pause these before bowel preparation for colonoscopy. Therefore, if a patient is to be investigated for IDA within two weeks, it would be appropriate to delay treatment until after the colonoscopy has been completed. There is no need to withhold oral iron before gastroscopy or CT colonography.

Various oral iron preparations are available in South Africa. Traditional oral iron salts (ferrous sulphate, ferrous gluconate and ferrous fumarate) are inexpensive, effective and safe, and they remain the standard therapies for IDA. Their use is supported by considerable clinical experience and observational data. In a pooled analysis of trial data, 72.8% of patients with IDA demonstrated a satisfactory response to an oral iron formulation, though rates of normalisation of Hb were lower with continued bleeding or clinically evident GI disease.[61] Traditionally, oral iron salts were taken as split doses, two or three times a day. More recent data suggest that lower doses, more infrequent administration, and sucrosomial and ferric iron formulations are as effective, while associated with lower rates of adverse effects and increased convenience.[62,63]

A Cochrane analysis in 2014 highlighted that the reviewed trials were of poor quality, but concluded that in comparison with placebo, oral IRT significantly improved Hb levels in IDA, and probably reduces blood transfusion requirements.[52] When given in standard doses, there do not appear to be significant differences in efficacy or adverse effects,[52] although side-effects may be lower with less than daily dosing.[64] Modified release preparations release iron in the more distal small bowel beyond the areas of most active assimilation – they do not enhance iron absorption[65,66] or reduce side-effects,[67] and their use is not recommended.

Iron absorption from oral preparations is determined by a complex interplay involving total body iron stores, the erythropoietic activity of the bone marrow, recent exposure of the small intestine to iron, and systemic inflammation.[68-72] Hepcidin is the most important inhibitor of iron absorption. Hepcidin levels follow a diurnal pattern and increase after oral iron intake, impairing fractional absorption of subsequent doses.[71,73] In the presence of inflammation, hepcidin pathway upregulation results in iron sequestration and subsequent iron-restricted erythropoiesis. The optimal drug, dosage and timing of oral IRT for adults with IDA are not clearly defined. Whatever agent and regime are chosen, it is essential to monitor the initial haematological response and modify it as appropriate with apparent therapeutic failure. The best option for patients with significant intolerance to oral IRT, usually GI disturbance, is also unclear.

The absorption of iron salts is significantly impaired if taken with food. Taking iron with meals can reduce bioavailability by up to 75%.[74] This necessitates iron being taken either in the fasting state first thing in the morning or in periods between meals during the day. It is not clear how soon after oral iron, food can be ingested, but the inhibitory effect of tea on iron absorption dissipates within 60 minutes.[75] Despite previous suggestions of benefit,[66] coadministration of vitamin C with oral IRT is not recommended – a recent large randomised controlled trial confirmed that it neither enhances the haematological response or rate of iron loading nor diminishes side-effects.[68]

There should be a prompt and measurable haematological response to the initiation of IRT, and early monitoring at four weeks should detect those patients not responding to or being intolerant of oral iron. Failure to respond to oral iron has many causes including non-compliance, malabsorption, systemic disease, bone marrow pathology, haemolysis, continued bleeding, and concurrent deficiency of vitamin B12 or folic acid. Regular monitoring is recommended to ensure an ultimate satisfactory response. The optimal interval is not clear but every four weeks until Hb is in the normal range seems reasonable. After normalisation of Hb, iron needs to be continued to replenish iron stores. If an adequate response to oral iron therapy is not observed, intravenous (IV) iron replacement must be considered.

9.2. Intravenous iron

IV iron replenishes body iron stores more rapidly than oral IRT. However, for most patients with IDA, this is not translated into a clinical benefit in terms of a rise in Hb.[55,76-78] The Hb response to

IV and oral iron is typically similar,[79] or marginally faster with IV iron. Therefore, the oral route is preferred on the grounds of cost and convenience with comparable efficacy.

The IV route for IRT may, however, be preferable from the outset in those with ongoing significant bleeding, malabsorption owing to GI disease, active IBD, the combination of ID and anaemia of inflammation, approaching surgery, or issues with administration (e.g. severe dysphagia) or compliance.[3,53,80] IV iron may also be indicated in those failing to respond to oral IRT owing to intolerance, pharmacodynamic failure, or continued bleeding. IV IRT is superior to continuing oral therapy in cases with IDA that failed to show significant Hb rise with oral IRT,[61] or who had ongoing menorrhagia.[53]

Blood transfusion is rarely required to treat IDA because, firstly, more patients with slowly developing anaemia adapt to the resulting physiological stress and, secondly, IV iron reliably produces a clinically meaningful Hb response. Transfusion should therefore be reserved for those with severe symptomatic and/or circulatory compromise. If used, packaged red cells should be transfused in accordance with established good practice guidelines. Since a unit of packed red cells contains only about 200 mg of elemental iron, it will not replenish the iron store deficit in severe IDA, so restrictive transfusion should be followed by adequate iron replacement.[48,81-88]

9.3. Monitoring

The optimal follow-up protocol after IRT remains to be established but, given the possibility of recurrent IDA indicating underlying disease, and the prevalence of persistent anaemia after IRT seen in some real-world studies,[89] periodic monitoring is advised. Once Hb has reached the normal range, a three-monthly blood count for 12 months and then six-monthly for 2 - 3 years would seem reasonable.

9.4. Safety

GI adverse effects such as nausea, diarrhoea and constipation are much more common with oral preparations. Infusion-related reactions are uncommon with modern IV iron preparations, but hypersensitivity-type and infusion reactions are commoner than with oral iron or placebo. Serious adverse reaction rates are low, however, and similar for oral and IV iron preparations.[90-92]

10. Disclaimer and limitations

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The recommendations do not establish a legal standard of care, nor are they intended to be referenced as evidence of a standard of care in legal proceedings. The implementation of the recommendations is further dependent on the affordability of the various modalities discussed in the respective healthcare settings. The treatments suggested are subject to availability and should be aligned with the treatment formularies applied in these settings. Further, as this is an evolving field of medical research, all guidance is subject to developments and new evidence that becomes available after its publication.

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11. Implementation and review

Implementation of the recommendations is aimed at various levels from individual practitioners to healthcare institutions, departments and regional, district, provincial and national platforms. It is intended that the guidance document spurs the development of centre-specific guidelines and that they are integrated into the relevant patient blood management protocols. It is advised that frequent monitoring of adherence to the recommendations is conducted and that the effect on blood product utilisation is assessed, using available data from the respective blood service.

This guidance document will be reviewed every five years by the SAGES guidelines sub-committee and, in the event of practice-changing evidence emerging, it may require revision. Users are advised to check for the latest information and ensure that the guidance remains appropriate and relevant to their clinical practice. The integration of the recommendations is intended to promote the optimal evaluation and management of patients with ID, regardless of the presence of anaemia.

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