Diagnosis and treatment of unexplained anemia with iron deficiency without overt bleeding

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ABBREVIATIONS AND DEFINITIONS

Anemia: Decreased blood hemoglobin levels (HgB) – a concentration less than 130 g/l (~ 8.1 mmol/l) for men and less than 120 g/l (~ 7.4 mmol/l) for non-pregnant women[1,2].

Iron deficiency (ID): Decreased iron content in the body, best assessed by a measurement of serum ferritin.

Iron deficiency anemia (**IDA**): Anemia caused by compromised erythropoiesis when low/empty iron stores are present.

Anemia due to inflammation (**inflammatory anemia (IA)**): Anemia due to inflammation (also known as **anemia of chronic disease** (**ACD**)) due to reduced absorption of iron and inadequate release of iron from iron stores.

Combined inflammatory anemia/iron deficiency anemia (mixed inflammatory and iron deficiency anemia (**CIIDA**)): Anemia due to inflammation with iron deficiency.

A**nemia with iron deficiency:** IDA or CIIDA.

IBD: Chronic inflammatory bowel disease.

Occult gastrointestinal bleeding: Positive stool bleeding test (fecal occult blood test (FOBT)).

Overt bleeding: Visible gastrointestinal bleeding.

Obscure bleeding: Persistent/recurrent bleeding from the gastrointestinal tract without a bleeding focus that is identified by gastroscopy or colonoscopy plus imaging of the small intestine. Obscure bleeding can be classified as obscure overt bleeding or obscure occult bleeding depending on whether blood is observable in the stool [6].

Bidirectional endoscopy: Performing both ileocolonoscopy and gastroscopy.

INTRODUCTION

Anemia is defined as a hemoglobin level less than the lower reference limit (for men, < 8.1 mmol/l; for non-pregnant women, < 7.4 mmol/l; and for pregnant women < 6.8 mmol/l) [1,2] and affects more than 2 billion people globally. Iron deficiency anemia is estimated to constitute approximately 50% of all anemias, with significant geographic variation [1,4].

In western societies, it is estimated that 1-2% of all adults have IDA [1]. Danish epidemiological studies observed IDA in less than 1% of 30- to 70-year-old men and approximately 4% of fertile women (for a list of frequencies in Denmark, see Table 1)

Worldwide, the main causes of IDA are malnutrition and gastrointestinal blood loss due to infections/infestations. The frequency of IDA depends on geography, gender, and age. In the western world, adolescent girls, menstruating women, pregnant and postpartum women, and blood donors have a particularly high risk of developing IDA [5] (for a list of causes, see Table 2).

PARACLINICAL DIAGNOSIS OF ANEMIA WITH IRON DEFICIENCY [7-10]

The hematological markers that indicate IDA are decreased hemoglobin with hypochromic and microcytic erythrocytes. Reticulocytic hemoglobin provides a snapshot of iron availability in the bone marrow, but direct testing of reticulocytic hemoglobin is not widely available.

Ferritin measurement is the best single blood parameter for diagnosing iron deficiency [9]. Each 1 µg/l of ferritin represents approximately 8 mg of stored iron. Combined measurements of ferritin and transferrin saturation, mean corpuscular volume (MCV) and red cell distribution width (RDW) only marginally increase the diagnostic certainty for iron deficiency [9]. Ferritin levels increase during inflammation, as an acute phase reactant the presence of inflammation can be assessed using C-reactive protein (CRP).

Ferritin levels < 30 µg/l without inflammation (i.e., normal CRP levels) are consistent with iron deficiency. With concomitant inflammation (i.e., elevated CRP levels), a ferritin level between 30 and 100 µg/l is consistent with iron deficiency. Ferritin levels > 100 µg/l exclude iron deficiency, independent of CRP levels [9-11].

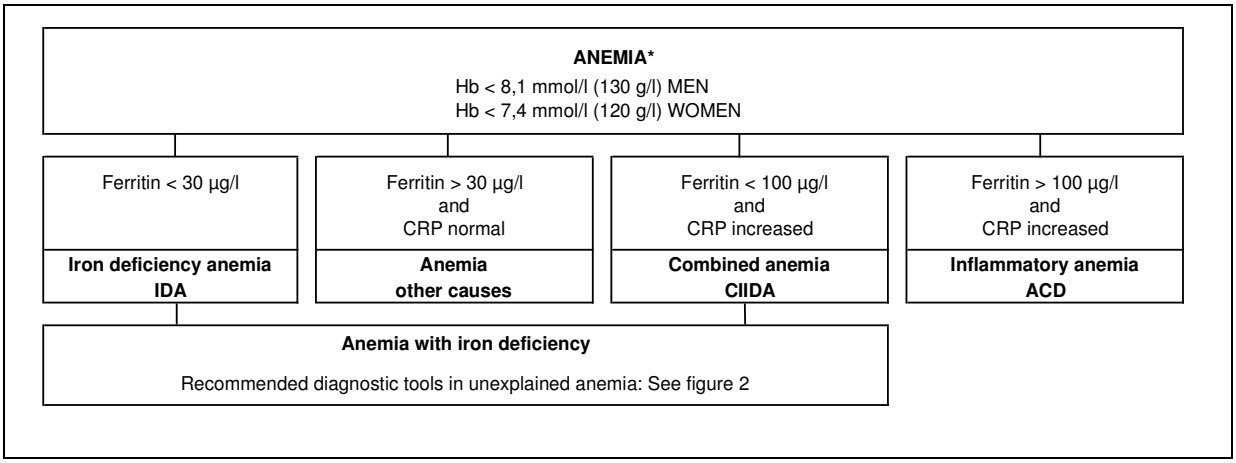

Figure 1. Diagnosis of anemia with iron deficiency.
** WHO definition of anemia [1,2]. IDA: iron deficiency anemia. CIIDA: combined inflammatory and iron deficiency anemia. ACD: anemia of chronic disease (inflammatory anemia). CRP: C-reactive protein.*

Measurements of plasma transferrin receptor fragments (soluble transferrin receptor) reflect the number of cells with high iron requirements, which are increased by iron deficiency and increased red cell production, but the measurement of sTfr is not generally possible. Measurements of iron and transferrin have no diagnostic value.

Generally, measurements of hemoglobin, ferritin, and CRP (see figure 1) can be used to diagnose anemia with iron deficiency, which can be classified into iron deficiency anemia (IDA) and combined inflammatory anemia and iron deficiency anemia (CIIDA).

Anemia with ferritin < 30 µg/l, regardless of CRP level:
Iron deficiency anemia (IDA).

Anemia with ferritin > 30 µg/l and normal CRP:
Anemia from other causes (cobalamin/folate deficiency, etc).

Anemia with ferritin < 100 µg/l and increased CRP:
Combined inflammatory anemia and iron deficiency anemia (CIIDA).

Anemia with ferritin > 100 µg/l and increased CRP:
Inflammatory anemia (IA or anemia of chronic disease – ACD).

Prevalence of iron deficiency anemia in Denmark
In Denmark, epidemiological studies conducted by Milman et al. described the frequencies of the following states, which are provided in Table 1: empty iron stores (ferritin < 13-16 g/l), low iron stores (ferritin < 32 – 34 µ/l), and iron deficiency anemia (HgB reduced, ferritin < 13 - 16 µ/l) [12-14].

PATHOGENESIS/ETIOLOGY OF ANEMIA WITH IRON DEFICIENCY
The pathogenesis of anemia is simply insufficient production or increased loss/destruction of erythrocytes (by hemorrhage or hemolysis) or the combination of reduced production and increased loss.

Decreased production (hyporegenerative anemia) has several possible causes, including the following:

1. a lack of iron, cobalamin, or folate;

2. infection/inflammation with increased apoptosis of erythrocyte precursors or decreased efficacy of erythropoietin (EPO) due to effects of cytokines, including tumor necrosis factor (TNF), interleukin-1 (IL-1) and interferon-γ (IFN-γ);

3. hematologic diseases and malignant bone marrow infiltration.

Table 1. Frequency of empty/low iron stores (iron deficiency) and iron deficiency anemia (IDA) in Denmark [12-14].

Sex and age (years)	Empty iron stores *	Low iron stores **	IDA***
Men[12,13]			
16 – 31	0.8%	5.3%	0%
40 – 70	0.4%	1.5%	0.16%
Women [12,14]			
16 – 19	14.7%	47.1%	14.7%
20 – 24	9.2%	35.6%	3.4%
25 – 31	8.6%	35.2%	3.7%
40 – 70 premenopausal	11.1%	29.9%	2.8%
40 – 70 postmenopausal	1.8%	5.7%	0.3%

*Empty iron stores (ferritin < 13 – 16 µg/l), ** low iron-stores (ferritin < 32 -34 µ/l, *** IDA (HgB low, ferritin < 13 -16 µ/l)

Table 2. Possible causes of IDA (Modified from Liu et al. [17] and Polin et al. [8]).

Decreased intestinal absorption	Increased need	Increased loss	Reduced release from iron stores
Inflammation Celiac disease Intestinal resection Bariatric surgery with gastric bypass Helicobacter pylori Atrophic gastritis Nutritional deficits (vegetarian)	Increased growth Pregnancy Treatment with erythropoietin	Intestinal bleeding: Esophagitis Gastritis Ulcers NSAID/ASA treatment Cancer/Polyps Ulcerative colitis Crohn's disease Vascular disease: Angiodysplasia Varices Portal hypertensive gastropathy Gastric vascular ectasia Hereditary angiodysplasia Hemorrhoids Diverticular disease Parasitic infection Other bleeding: Menstruation/menorrhagia Macroscopic hematuria Recurrent epistaxis Recurrent blood donation Trauma, including surgery	Inflammation

Anemia with increased but insufficient bone marrow red blood cell production (regenerative anemia) is observed in bleeding (1 ml of blood is equivalent to 0.5 mg of iron) or hemolysis [15,16]. Reticulocyte counts will be reduced/increased by hyporegenerative/regenerative anemia, respectively.

Anemia can be caused by a combination of inadequate production and increased loss/destruction of red blood cells; for example, in chronic inflammatory bowel diseases, chronic inflammation reduces erythrocyte production due to decreased iron absorption from the small bowel, reduced release of iron from iron stores, and increased loss of red cells due to bleeding.
A general overview of the causes of iron deficiency and anemia with iron deficiency is shown in Table 2. Iron deficiency can be a multifactorial condition; many of these factors can be characterized as likely contributors but not necessarily the sole cause of iron deficiency in a particular patient.

MALIGNANT DISEASE AS THE CAUSE OF ANEMIA WITH IRON DEFICIENCY

Iron deficiency anemia is associated with a risk of malignancy of the gastrointestinal tract, especially colon cancer. In a U.S. cohort, the prevalence of gastrointestinal malignancy was 0.2% overall but 6% in those with iron deficiency anemia [18]. In heterogeneous studies of patients with iron deficiency anemia, the incidence of malignant disease was 8-15% [19-23].
In a large English population with iron deficiency anemia (more than 600 patients), the frequency of upper gastrointestinal cancer was 1/7 of colon cancer [23].
Small bowel tumors are rare. Small bowel tumors were found in an average of 3.5% of 1194 patients in different studies that investigated obscure bleeding using capsule endoscopy. These studies are influenced by selection bias and are not representative of IDA patients in general. Among patients with iron deficiency anemia, the incidence of small bowel tumors is 0% [23,24] to 0.9%. [22]

Retrospective investigations have reported varying frequencies of extra-intestinal malignancy, which was found in 3.5% of patients older than 50 years during a 5-year follow-up after an initial negative bidirectional endoscopy that was performed because of IDA [23].
Advanced age, male sex, and low hemoglobin levels are associated with an increased risk of malignancy in iron deficiency anemia [20,22,23].
The use of NSAIDs, ASA, or antithrombotic therapy in IDA patients does not reduce the risk of concomitant colon cancer or gastric

cancer [22]. The following factors have not been shown to be useful in predicting the risk of malignancy among patients who have been diagnosed with IDA: weight loss, abdominal pain, bowel disorders, gastrointestinal malignancy among first-degree relatives and stool testing for occult bleeding [22,24,25].

BENIGN GASTROINTESTINAL CAUSES OF ANEMIA WITH IRON DEFICIENCY

Premenopausal women

Women of childbearing potential have physiologically lower hemoglobin and ferritin levels (from menstrual blood loss or the effects of pregnancy or the postpartum period). This difference is reflected in the respective reference ranges (see the section defining anemia in this guideline). In addition, some women have heavy menstrual bleeding. The frequency of menorrhagia in premenopausal women with IDA has been reported to be 35-65% [26,27].

The physiologically lower hemoglobin levels in premenopausal women do not, of course, rule out the possibility that premenopausal women with IDA and menorrhagia may simultaneously have an additional gastrointestinal cause of IDA. This condition has been observed in several retrospective studies and is usually caused by iron malabsorption, for example, celiac disease, atrophic gastritis, or H. pylori infection, and is rarely caused by ulcers or malignancy [28-30]. Menorrhagia and a benign gastrointestinal cause of IDA are simultaneously observed in 20-35% of premenopausal women with IDA [26,27,31].

The relative frequency of atrophic gastritis among premenopausal women with IDA [7,11] does not justify the routine use of gastroscopy in this group because regardless of the gastroscopy findings, the treatment is iron supplementation. Furthermore, there is no evidence that *H. pylori* eradication in this specific patient group has an effect on IDA.

Overall, all women > 40 years of age who have unexplained iron deficiency anemia should be offered bidirectional endoscopy (colonoscopy and gastroscopy) [3,27,29,31].

Gastrointestinal bleeding sources

Gastrointestinal ulcerations

Recent studies of iron deficiency anemia patients have reported a gastrointestinal ulcer rate of 6% to 7% [22,23]. This prevalence is considerably less than the approximately 30% rate reported in studies between 1986 and 1998 [19,20,32,33] and most likely represents a true change in prevalence in the present era.

Angiodysplasia

Angiodysplasia is estimated to amount for 3-5% of cases with overt or occult GI bleeding [19,34] and can be located in the colon (approximately 80% of cases), small intestine (approximately 15% of cases), or stomach [35]. Angiodysplasia of the colon is almost always located in the cecum or the right colon [36], whereas angiodysplasia of the small intestine in western populations is primarily located in the duodenum and secondarily in the jejunum [37-40].

Other sources of bleeding

Unrecognized chronic inflammatory bowel disease, portal hypertensive gastropathy, hereditary telangiectasia and gastric antral vascular ectasia (GAVE) are other less common causes of iron deficiency anemia with no apparent gastrointestinal bleeding.

Drugs

Several drugs may be ulcerogenic in the gastrointestinal tract, especially non-steroidal anti-inflammatory drugs (NSAIDs) and aspirin (ASA).

NSAIDs and ASA are widely used and are associated with a wide spectrum of changes in gastrointestinal integrity and function [41]. Hemorrhagic erosion is frequently observed, and gastroduodenal ulcer disease is observed in up to 40% of patients receiving long-term NSAID treatment without ulcer prophylaxis [42].

Exposure to NSAIDs and ASA increases gastrointestinal blood loss in patients without gastrointestinal disease [43], and NSAID–induced chronic bleeding from the small intestine may contribute to iron deficiency anemia in patients with rheumatoid arthritis [44]. NSAIDs are associated with colitis and can activate inflammatory bowel disease and trigger ulceration in the colon, particularly in elderly individuals [41].

Antithrombotic drugs, alone or in combination, are increasingly used to treat and prevent thromboembolism after the placement of artificial heart valves or coronary stents[45]. Antithrombotic therapy increases blood loss from gastrointestinal lesions (e.g., ulcers or angiodysplasia). The risk varies depending on the drugs that are used [46].

Numerous series of interactions between antithrombotic medications and other types of medication (e.g., NSAIDs + warfarin, NSAIDs/ASA + prednisolone) have been reported; these interactions also increase the risk of GI bleeding.

The range of available antithrombotic medications has increased, and these medications are often used in combination. Risk-benefit assessments for individual patients can be improved by coordinated consultation with a cardiologist [47,48].

Malabsorption

Celiac disease

The frequency of celiac disease varies between 2-15%, depending on patient selection and geographic location [23,49-54]. The prevalence of celiac disease among patients with iron deficiency anemia in European studies is approximately 5% [23,55].

Atrophic gastritis

Atrophic gastritis may be accompanied by hypochlorhydria and can inhibit iron absorption. The incidence of atrophic gastritis in asymptomatic patients with iron deficiency anemia and macroscopically normal findings at gastroscopy and colonoscopy is 20% -27% [21,56,57]. Typically, patients *do not* simultaneously have B12 deficiency. Frequently, elevated serum gastrin and the positive parietal antibodies are found [57]. Patients with iron deficiency anemia and atrophic gastritis tend to be relatively young (median age ~ 45 years).

Gastric bypass and gastric resection

Resection of the stomach and gastric bypass can be accompanied by iron malabsorption and iron deficiency anemia [16,58,59].

Iron deficiency is found in 30% to 40% of obese subjects scheduled for bariatric surgery, and anemia is found in 10-15% [16]. This connection is supported by a direct association between body mass index and iron deficiency in both pre-and postmenopausal women [60]. Insufficient nutrition and chronic inflammation with

increased hepcidin synthesis is believed to contribute to this phenomenon [16,61].

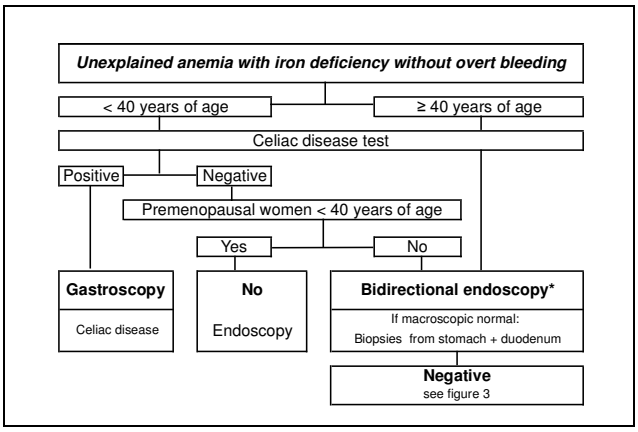

Figure 2. Diagnostic work-up of unexplained anemia with iron deficiency without overt bleeding.
Celiac disease test: Measurement of transglutaminase antibodies and IgA.
** Referring to National Board of Health's procedure to diagnose colorectal cancer 2012*[3]

Bariatric surgery can use two mechanisms. The first involves either irreversibly reducing gastric capacity by removing part of the stomach or reversibly reducing gastric capacity with a ribbon that is laced into the ventricle (gastric banding). The second principle, used in surgical bypass, ultimately leads foods to bypass the duodenum and a segment of the jejunum (gastric bypass).
The most common form of bariatric surgery in Denmark today is a combination of reducing the stomach size and performing a bypass using a Roux-en-Y loop (Roux-en-Y gastric bypass). The reduced ventricular size causes hypochlorhydria, thereby reducing iron absorption.

After bariatric surgery, iron deficiency is observed in 12% to 60% of patients, and anemia is found in 10% to 54% of patients, likely as a result of a reduced intake of iron-containing foods, reduced solubilization of ferric iron due to reduced acid secretion, and Roux-en-Y-related bypass of the duodenum and upper part of the jejunum, where the absorption of iron takes place [16,58].
After bariatric surgery, patients require lifelong monitoring of iron turnover and oral iron supplementation. Intravenous iron may be necessary if oral iron substitution is ineffective.

Helicobacter pylori infection
Iron deficiency and iron deficiency anemia are observed with increased frequency in patients infected with *H. pylori* [62] The prevalence of *H. pylori*-triggered iron deficiency anemia is, however, uncertain.

Iron is essential for the growth of *H. pylori*, and it has been shown that H. pylori absorbs both heme iron from erythrocytes and non-heme iron from lactoferrin [63-65]. Furthermore, *H. pylori* infection is associated with a reversible reduction in the gastric secretion of ascorbic acid [66]. Therefore, *H. pylori* infection is associated with both increased iron consumption and, theoretically, impaired iron absorption.
A meta-analysis found that *H. pylori* infection is associated with a 2.8-fold increased risk of iron deficiency anemia [62]. Two meta-analyses have compared the efficacy of oral iron therapy alone versus oral iron therapy and H. pylori eradication in H. pylori-positive patients with iron deficiency anemia [67,68]. Both studies found that combined therapy (with iron and H. pylori eradication) was associated with a significant increase in hemoglobin (by up to 0.8 mmol/l) compared with iron therapy alone.

One could argue that these studies were mainly conducted in Asian populations, which may differ from Western populations in this context. Furthermore, gastroscopy was not performed in many of the include
ed studies. Thus, some of the identified effect may result from healing of the ulcer rather than helicobacter eradication.

YIELD OF GASTROINTESTINAL ENDOSCOPY
Colonoscopy and gastroscopy
The diagnostic yields of gastroscopy and colonoscopy have been reported to be 35-55% and 25-30%, respectively[19,32,69,70].

Concurrent positive findings on both upper and lower endoscopy have been reported in 1-23% of patients [19,32,69,70], with a potential bleeding source identified in 9% to 23% of cases where initial gastroscopy or colonoscopy revealed a potential bleeding source [69,70].

During colonoscopy, the following positive findings are regarded as evident bleeding sources: cancer, polyps, angiodysplasia and chronic inflammatory bowel disease (IBD).

Positive findings on gastroscopy include bleeding sources (ulcerations, angiodysplasia, and cancer) and malabsorption, which is not evident during gastroscopy but requires an additional biopsy or biochemical tests (e.g., for celiac disease or atrophic gastritis).

Capsule endoscopy
The diagnostic yield of capsule endoscopy after negative bidirectional endoscopy has been calculated to be

67% (95% confidence interval: 61% -72%) in a meta-analysis of 24 retro- and prospective studies (1960 patients) of patients with IDA [71]. However, both the retro- and prospective studies were heterogeneous and were generally subject to selection bias. The most frequent findings were angiodysplasia in the small intestine (24.5%), inflammatory lesions (10.5%) and tumor/polyps (3.5%).

It is not clear whether capsule endoscopy improves the outcome of patients with IDA. Anemia-inducing angiodysplasias in the small intestine without overt bleeding might be better treated with iron supplements and reductions in anticoagulant and antiplatelet therapy than with endoscopic or surgical therapy. However, data to support this recommendation are lacking.

A blinded randomized prospective study did not find differences in the need for blood transfusion, hospitalization, or mortality 12 months after randomization to capsule endoscopy or dedicated small bowel contrast radiography in patients with obscure bleeding and
a negative push enteroscopy [40]. In another study, recurrent IDA was found in 8% of patients 8-18 months after capsule endoscopy [72]. A recent Irish retrospective study of 65 patients who had un

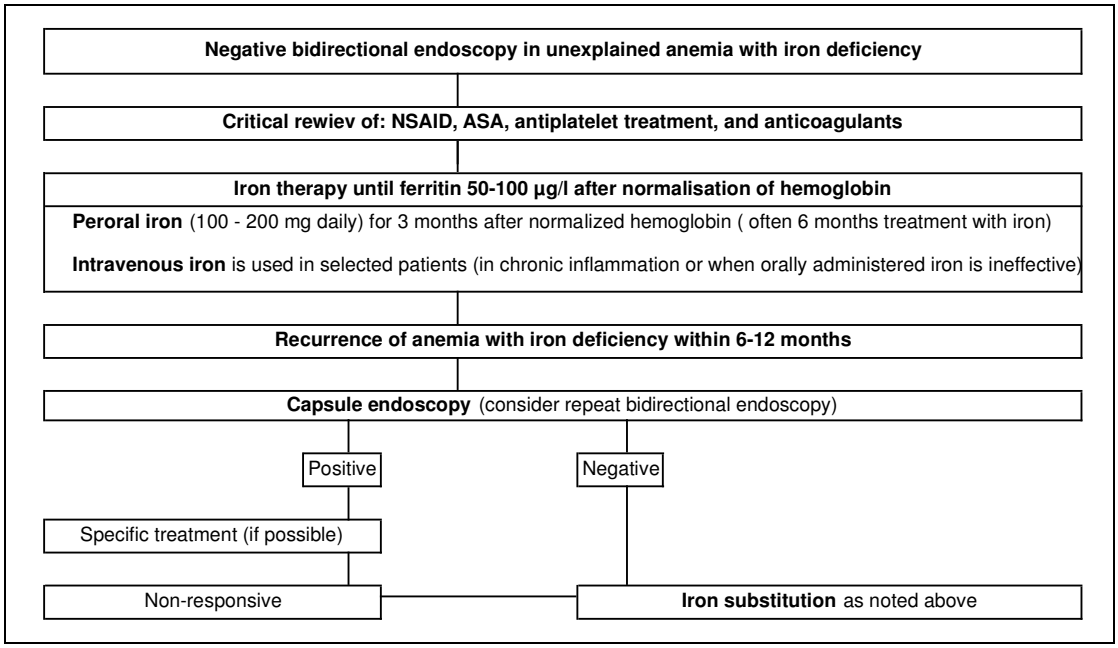

Figure 3. Diagnostic and therapeutic algorithm for unexplained anemia with iron deficiency after negative bidirectional endoscopy according to figure 2.

dergone capsule endoscopy for IDA (with findings in 71%) showed that 42% were still anemic, regardless of the capsule endoscopy findings; only 6 of the 22 patients who underwent further testing or interventions were cured of anemia [73]

Negative investigational work-up

A negative gastrointestinal evaluation for IDA is common and occurs in 14-60% of patients [19,20,23,24,32,74] The reported frequency depends on the cause of IDA, as well as the examination method, the criteria for performing the investigation, and the patient population.

DIAGNOSTIC STRATEGY FOR UNEXPLAINED ANEMIA WITH IRON DEFICIENCY – CLINICAL RECOMMENDATIONS

- Serological celiac disease screening should be performed (transglutaminase antibody (IgA type) and IgA; if decreased IgA is found, the transglutaminase antibody (IgG type) should be measured (EN2b, RG B)).

- Bidirectional endoscopy should be performed (EN2a, RG B)
  Exceptions to this recommendation include the following patient populations:
  - Premenopausal women under the age of
  - Men and women < 40 years with newly diagnosed celiac disease (EN2b, RG B).
  - The presence of transfusion-dependent anemia, a hereditary predisposition to early-onset colorectal cancer, or unintentional weight loss indicates that the two aforementioned exceptions should be disregarded, and bidirectional endoscopy should be performed.

- Bidirectional endoscopy should be performed
  - Regardless of the patient's history of treatment with NSAIDs/ASA or antithrombotic therapy (EN3b, RG B).
  - Regardless of the outcome of any stool testing for occult bleeding (EN3b, RG B).
  - Ileocolonoscopy should be performed with a focus on identifying bleeding sources, including tumors/polyps, ulcers, angiodysplasia and inflammatory bowel disease (EN3b, RG B).
  - Gastroscopy should be performed to identify bleeding sources, specifically ulcers, mucosal inflammation, angiodysplasia and portal gastropathy. If no definite bleeding source is found, then biopsies should be obtained to test for celiac disease, atrophic gastritis and H. pylori infection (EN3b, RG B).

- In patients who require bidirectional endoscopy, it might be advantageous to perform ileocolonoscopy first, followed by gastroscopy; biopsies for malabsorption may be avoidable in some cases where a convincing source of bleeding is found during colonoscopy, as colon cancer is much more common than upper gastrointestinal cancer (EN2a, RG B).

- The yield of capsule endoscopy is relatively low, and most patients seem to be best served by iron supplementation and a critical review of NSAID, ASA and antithrombotic therapy, independent of capsule endoscopy findings (EN4, RG C).

- Capsule endoscopy is indicated if there is a rapid recurrence of iron deficiency anemia after iron therapy with full iron stores, if there is no suspicion of small bowel stenosis (EN4, RG C).

- The patient's medications should be reviewed critically, with particular care taken to evaluate the use of NSAIDs, ASA, and antithrombotic therapy, as well as potential drug interactions. A strategy for further antithrombotic therapy can be planned in consultation with a cardiologist (EN4, RG C).

- Evaluations for extra-intestinal malignancy, for instance CT of the thorax and abdomen, may be considered after negative bidirectional endosif other signs that indicate malignancy are present (EN4, RG B).

IRON THERAPY

Any cause of IDA found on diagnostic assessment must be treated in a targeted fashion. In addition, iron supplementation should be initiated in patients with iron deficiency anemia [7,75,76].

The treatment goal is the normalization of hemoglobin and replenishment of iron stores.

Oral iron supplementation can be used if inflammation (leading to reduced intestinal iron absorption) and signs of intestinal malabsorptive disease are absent.

Generally, a dose of 100 to 200 mg elemental iron (ferric-salts) in 2 divided daily doses is recommended . [7,75]. Low doses or alternate-day dosing can be used (because absorption of the administered dose is increased by reduced iron stores) to decrease the incidence of adverse effects, such as nausea, abdominal pain, and constipation/diarrhea [7].
If oral iron supplementation is effective, increased erythropoiesis (increased reticulocyte counts) is expected within 3 to 10 days, with normalization of hemoglobin levels within 6 to 12 weeks. Replenishment of iron stores will usually require an additional 12 to 16 weeks of oral iron supplementation [7,75]. The total oral iron treatment course should thus be approximately 6 months to ensure that anemia has resolved and iron stores are replenished.

Intravenous iron treatment is used if there is prolonged inflammation (e.g., active inflammatory bowel disease), malabsorption or reactions to/lack of intake of oral iron, and in situations where a rapid increase in iron stores is needed [77,78] The various intravenous iron preparations are believed to be equally effective, but two preparations (ferric carboxymaltose isomaltoside and iron) may be administered at 20 mg/kg body weight over 15 to 60 minutes.

The total iron requirements (mg) can be calculated [78] from the measured hemoglobin (mmol/l), the desired (target) hemoglobin (mmol), the weight (kg) and the replenishment requirement for iron stores (approximately 10 -15 mg/kg body weight[79]), using the following equation:

- total iron needs (in mg) = 3.84 x weight x (desired hemoglobin - measured hemoglobin) + storage-iron

A simplified estimate is provided by the following equation:

- total iron needs (in mg) = weight x (4 x the desired hemoglobin increase + 10).

Clinical recommendations

- Treat perorally with 100-200 mg of elemental iron daily (reduce the dose if there are side effects) (EN2b, RG B).

- Reticulocytes should be measured after 1 week and should increase.

- Continue with iron treatment until 3 months after the HgB level has normalized (EN2b, RG B)

- Intravenous iron therapy is used if the oral treatment lacks efficacy, causes side effects, or if intestinal malabsorption or prolonged inflammation is present (EN1B, RG A).

CHRONIC INFLAMMATORY BOWEL DISEASE (IBD)

Anemia is the most common extraintestinal complication of chronic inflammatory bowel diseases such as Crohn's disease (CD) and ulcerative colitis (UC), due to inflammation that causes a lack of iron absorption, decreased iron release from iron stores, and blood loss from the gut. Anemia in IBD is relatively rarely caused by cobalamin/folate deficiency or as a side effect of immunosuppressive treatment [80,81]

In a consecutive prospective cohort investigation of 429 Scandinavian outpatient IBD patients, 19% (23% CD, 14% UC) had anemia; approximately 90% of patients with anemia had either pure iron deficiency anemia (20%) or combined inflammatory anemia and iron deficiency anemia (68%)[82]. A lower anemia frequency of 6% (9% CD, 5% UC) was found in a Swedish IBD population [83].

Active IBD inflammation usually causes anemia with iron deficiency, and intravenous iron replacement is usually recommended due to the inflammation-induced lack of intestinal iron absorption [80].
In IBD-related anemia, unexplained anemia with iron deficiency is usually not present; however, the detection of iron deficiency anemia in an IBD patient who is in remission and does not have visible bleeding should prompt a strategy for evaluation and treatment following the same guidelines as if the patient did not have IBD.

Clinical recommendations

- IBD patients without inflammatory activity and no visible bleeding from the gastrointestinal tract should be evaluated according to the same guidelines as patients who do not have IBD.

- In active IBD with inflammation and anemia and iron deficiency, iron supplementation with intravenous iron is recommended.

IRON METABOLISM AND THE FORMATION AND DEGRADATION OF ERYTHROCYTES [8,15,16,84].

A healthy adult contains 2-6 g of iron in the form of iron bound to hemoglobin (70%), enzymes and myoglobin (10%), iron in plasma (transferrin - iron) (0.1%), and iron stores (20%) that are bound to ferritin in the macrophages of the reticuloendothelial system and in hepatocytes.

There is no mechanism to regulate iron loss, but usually iron absorption and iron loss are equivalent (1-2 mg/day).

Table 3. Evidence level for clinical recommendations. Evidence levels (EN, 1 to 5) and recommendation grades follow the guidelines provided by the Centre of Evidence-based Medicine, University of Oxford.

	Level of evidence	Recommendation
Serological testing for celiac disease with transglutaminase antibody (IgA type) and IgA; if IgA deficiency is present, the IgG type transglutaminase antibody should be measured.	**2b**	**B**
Bidirectional endoscopy (EN2a) should be performed. Exceptions to this recommendation include: • Premenopausal women < 40 years of age (EN2b). • Men and women < 40 years old with newly diagnosed celiac disease (EN2b). ○ If there is transfusion-dependent anemia, a hereditary predisposition to early-onset colorectal cancer, or unintentional weight loss, these two exceptions should be disregarded, and bidirectional endoscopy should be performed.	**2a/2b**	**B**
Bidirectional endoscopy is performed: • Regardless of the patient's history of NSAIDs, ASA, or antithrombotic therapy use. • Regardless of the outcome of any stool testing for occult bleeding. • Ileocolonoscopy should be performed with a focus on identifying bleeding sources, including tumors/polyps, ulcers, angiodysplasia and inflammatory bowel disease. • Gastroscopy is performed with the aim of identifying bleeding sources, such as ulcers, mucosal inflammation, angiodysplasia and portal gastropathy. ○ If no convincing bleeding source is found, biopsy should be performed to test for celiac disease, atrophic gastritis and H. pylori infection.	**3b**	**B**
When performing bidirectional endoscopy, it may be useful to perform ileocolonoscopy first, followed by gastroscopy, as gastroscopy may be avoidable if a definite cause of lower bleeding is found. Colon cancer is much more common than upper gastrointestinal cancer in IDA.	**2a**	**B**
Examination of the small intestine (with capsule endoscopy, CT or MRI enterography) is not recommended routinely after negative bidirectional endoscopy (EN 4, RG C) but should be considered when symptoms or serological markers suggest malignant or inflammatory disease (e.g., involuntary weight loss, abdominal pain or elevated acute – phase proteins)	**4**	**C**
The yield of capsule endoscopy is relatively low, and most patients will be best served by iron supplementation and a critical review of NSAID, ASA and antithrombotic therapy, independent of capsule endoscopy findings.	**4**	**C**
Capsule endoscopy is indicated if there is a rapid recurrence of iron deficiency anemia following iron therapy in patients who have full iron stores and no suspicion of small bowel stenosis.	**4**	**C**
Evaluation for extra-intestinal malignancy (e.g., with CT of the thorax and abdomen), may be considered after negative bidirectional endoscopy if other evidence of malignancy is present.	**4**	**C**
All patients' medications should be critically reviewed, especially NSAIDs, ASA and antithrombotic therapy, as well as potential drug interactions. A treatment strategy for antithrombotic therapy may be planned in co-operation with a cardiologist.	**4**	**C**
Orally administered iron treatment should consist of 100-200 mg of elemental iron daily (reduce the dose if there are side effects). Continue oral iron treatment until 3 months after the HgB level normalizes to ensure adequate iron stores.	**2b**	**B**
Intravenous iron therapy is preferred when oral iron therapy is ineffective or causes side effects, or when intestinal malabsorption or prolonged inflammation is present.	**1b**	**A**

Iron absorption takes place mainly in the duodenum and proximal jejunum. Iron is exported out of enterocytes through *the iron gate* - the membrane-bound ferroportin - and bound to the transport protein transferrin.

Iron bound to transferrin (which has two binding sites for iron) is transported through the bloodstream to all cells and especially to bone marrow erythroid progenitors. There is a very effective means of recycling, and each day, 20-30 mg iron/day is transported by the transferrin-iron complex. The vast majority of this iron is derived from macrophages that phagocytose old red blood cells.

Iron turnover has 3 sources of iron inputs to transferrin in the circulation: (i) iron that is recycled from phagocytosed erythrocytes by macrophages (by far the most important), (ii) hepatocyte iron stores, and (iii) the intestinal absorption of iron.

Ferroportin is found on enterocytes, hepatocytes and macrophages. Hepcidin controls iron turnover from these three cell types via ferroportin because hepcidin binds to ferroportin molecules on the cell surface, and the ferroportin-hepcidin is internalized and degraded. This change reduces *the iron gate* on the cells, and iron export to transferrin is stopped.

Hepcidin formation occurs in the liver, and hepatocyte synthesis is controlled in part by the iron saturation of transferrin, with increased production in cases of iron overload or inflammation and decreased formation in the presence of iron deficiency .

In inflammation, increased interleukin-6 (IL-6) levels increase the hepatic synthesis of hepcidin. Increased hepcidin results in decreased iron export from macrophages/hepatocytes (iron stores) and enterocytes. In inflammation, there is thus impaired intestinal absorption of iron simultaneously with compromised release and export of intracellular iron from the iron stores. In inflammation, there is functional iron deficiency with an insufficient supply of iron for erythropoiesis in bone marrow.

IRON ABSORPTION TEST

Evaluation with an iron absorption test can indicate a lack of response to oral iron therapy and definitively establish that intestinal malabsorption of iron is present. However, in most cases, the result of the test does not influence the final treatment strategy for iron supplementation (oral iron substitution or intravenous iron replacement after failure of oral iron therapy).

Detection of an increase in plasma iron (P-iron) after oral iron administration reflects intestinal iron absorption [85], and an increase in P-iron is a sensitive marker of body iron stores [86,87].

Patients with anemia and low P-iron secondary to chronic disease (inflammation anemia) differ from patients with pure iron deficiency anemia in that they do not respond with a corresponding increase in P-iron during an iron absorption test, due to the inflammation-mediated decrease in intestinal iron absorption. [86,87]

Method

Current studies show variations in selected iron dose, time interval of P-iron measurement, and recommended diagnostic threshold used.

For the iron absorption test, the patient must fast (minimum 8 hours). Because of the significant diurnal variations in P–iron, the test should be conducted between 8 and 10 o´clock in the morning [86,87]. The test begins with a measurement of P-iron. Thereafter, the patient should consume100 mg of ferrous sulfate with 100-200 ml of water. Two hours after iron intake, P-iron measurements should be obtained again.

Interpretation

When the P-iron increases to greater than 18 µmol/l, the patient most likely has normal iron absorption [86-89]. If patients with an increase in P-iron to over 18 µg/l do not respond sufficiently to oral iron therapy, patient non-compliance or ongoing iron losses should be considered.

When the P-iron level increases by less than 18 µmol/l, the patient most likely has iron malabsorption. This condition is observed in malabsorptive small bowel disease (celiac disease), following certain surgical procedures (including disconnection of the proximal small intestine, small bowel resection, and gastric resection with consequent hypochlorhydria), atrophic gastritis and inflammation due to acute and chronic inflammatory diseases/cancer [86,87].

SUMMARY

A general overview is given of the causes of anemia with iron deficiency as well as the pathogenesis of anemia and the paraclinical diagnosis of anemia.

Anemia with iron deficiency but without overt GI bleeding is associated with a risk of malignant disease of the gastrointestinal tract; upper gastrointestinal cancer is 1/7 as common as colon cancer. Benign gastrointestinal causes of anemia are iron malabsorption (atrophic gastritis, celiac disease, chronic inflammation, and bariatric surgery) and chronic blood loss due to gastrointestinal ulcerations.

The following diagnostic strategy is recommended for unexplained anemia with iron deficiency: conduct serological celiac disease screening with transglutaminase antibody (IgA type) and IgA testing and perform bidirectional endoscopy (gastroscopy and colonoscopy). Bidirectional endoscopy is not required in premenopausal women < 40 years of age.
Small intestine investigation (capsule endoscopy, CT, or MRI enterography) is not recommended routinely after negative bidirectional endoscopy but should be conducted if there are red flags indicating malignant or inflammatory small bowel disease (e.g., involuntary weight loss, abdominal pain or increased CRP).

Targeted treatment of any cause of anemia with iron deficiency found on diagnostic assessment should be initiated. In addition, iron supplementation should be administered, with the goal of normalizing hemoglobin levels and replenishing iron stores. Oral treatment with a 100-200 mg daily dose of elemental iron is recommended (lower dose if side effects), but 3 – 6 months of oral iron therapy is often required to achieve therapeutic goals. Intravenous iron therapy is used if oral treatment lacks efficacy or causes side effects or in the presence of intestinal malabsorption or prolonged inflammation.

Three algorithms are given for the following conditions:

a) the paraclinical diagnosis of anemia with iron deficiency;
b) the diagnostic work-up for unexplained anemia with iron deficiency without overt bleeding; and
c) how to proceed after negative bidirectional endoscopy of the gastrointestinal tract.

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