Anemia as a Problem: GEH Approach

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Keywords

Iron deficiency · Anemia · Gastroenterologist · Endoscopy

Abstract

Background: Anemia is present in almost 5% of adults worldwide and accompanies clinical findings in many diseases. Diseases of the gastrointestinal (GI) tract and liver are a common cause of anemia, so patients with anemia are often referred to a gastroenterologist. **Summary:** Anemia could be caused by various factors such as chronic bleeding, malabsorption, or chronic inflammation. In clinical practice, iron deficiency anemia and the combined forms of anemia due to different pathophysiological mechanisms are most common. Esophagogastroduodenoscopy, colonoscopy, and the small intestine examinations in specific situations play a crucial role in diagnosing anemia. In anemic, GI asymptomatic patients, there are recommendations for bidirectional endoscopy. Although GI malignancies are the most common cause of chronic bleeding, all conditions leading to blood loss, malabsorption, and chronic inflammation should be considered. From a gastroenterologist's perspective, the clinical spectrum of anemia is vast because many different digestive tract diseases lead to bleeding. **Key Messages:** The

gastroenterological approach in solving anemia's problem requires an optimal strategy, consideration of the accompanying clinical signs, and the fastest possible diagnosis. Although patients with symptoms of anemia are often referred to gastroenterologists, the diagnostic approach requires further improvement in everyday clinical practice.

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Introduction

The largest number of patients who come to the gastroenterologist is referred by the general practitioner, mostly due to gastrointestinal (GI) symptoms, manifest bleeding whose cause needs to be determined, or due to anemia whose cause is unknown [1]. Diseases of the GI tract often lead to anemia, which is why patients with iron deficiency anemia (IDA) are often referred to gastroenterologists for further examination [1–3]. Usually, a lot of time could be lost, so it is sometimes too late to make a definitive diagnosis [4]. IDA as a consequence of occult bleeding can be a consequence of benign chronic diseases but it is even more critical to exclude malignancies. The American Gastroenterological Association (AGA) de-

finds occult GI bleeding as the initial presentation of a positive fecal occult blood test (FOBT) and/or IDA without visible blood loss confirmed by the patient or physician [5, 6]. Nearly any damage to the GI tract leads to a mucosal lesion that can bleed enough to lead to occult blood loss and cause IDA. From the gastroenterologist's point of view, the clinical spectrum of IDA is very wide because a large number of different lesions from distinct locations can bleed in an occult way [7–9] (Table 1).

Anemia can also occur due to overt GI bleeding that can be clinically presented as hematemesis, melena, or hematochezia. The diagnostic decision in these conditions is more straightforward because IDA, with accompanying symptoms, indicates the most probable cause of bleeding. In chronic, occult GI blood loss, bleeding is not visible and is clinically detected as an IDA or positive FOBT. In both cases, accurate diagnosis is crucial to provide timely, optimal treatment and prevent delays in diagnosis, which is essential for the prognosis and outcome of administered treatment to these patients. IDA is traditionally attributed to chronic GI bleeding in all patients, which requires further examinations of the GI tract, including the suspicion of colorectal cancer (CRC). The only exception is premenopausal women, where a gynecologist is necessary to assist [6, 8]. After the patient with IDA is referred to gastroenterologists, they must choose the appropriate diagnostic procedures for examining the GI tract. If any, accompanying symptoms help select and order examinations, but the lack of a universal diagnostic approach in IDA patients without GI symptoms remains.

Today, it is considered that anemia is present in 2–5% of the general population and that among them, there are 4–13% of those who have some of the gastroenterological diseases [10–12]. The most common type of anemia in gastroenterological diseases is IDA [3, 13], which is associated with manifest bleeding of varying degrees from those most severe, where hospital admission is obliged, to mild anemia or those where the cause is difficult to detect, despite the use of all endoscopic examination methods. IDA associated with GI disorders can significantly reduce the life quality, lead to various symptoms, and maybe indicate hospitalization [14]. Depending on the degree of anemia, patients have mild or more pronounced disorders, headaches, dizziness, and pallor. In contrast, gastroenterological symptoms depend on the GI tract involved and suggest that further endoscopic examination be made [15, 16]. Guidelines for the diagnosis and treatment of IDA are available for inflammatory bowel disease (IBD) [3]. In contrast, procedures for the diagnosis and treat-

Table 1. Etiology of IDA regarding GI segments

Segment	Blood loss	
	acute	chronic
<i>Esophagus</i>		
Mallory-Weiss tear	+	
GERD	+	⊕
Esophagitis		+
Drug-induced erosions/ulcers	⊕	+
Caustic lesions/foreign bodies	+	
HH	+	⊕
Achalasia		+
Variceal bleeding	⊕	+
Esophageal ulcer	⊕	+
Esophageal cancer	+	⊕
<i>Stomach and duodenum</i>		
Peptic ulcer disease	⊕	+
Drug-induced erosions/ulcers	+	+
Variceal bleeding	+	
Portal hypertensive gastropathy and GAVE	+	⊕
Angiodysplasia	⊕	+
Polyps	+	⊕
Gastric cancer	+	⊕
<i>Small intestine</i>		
CD		+
Angiodysplasia	⊕	+
IBD	+	+
Polyps	+	⊕
Diverticula	⊕	+
Malignancies	+	⊕
<i>Colon</i>		
Malignancies (left hemicolon)	+	+
Malignancies (right hemicolon)	+	⊕
Polyps	+	⊕
Diverticula	⊕	+
Angiodysplasia	⊕	+
IBD	+	⊕
Benign rectal diseases	+	+

⊕, predominates; GAVE, gastric antral vascular ectasia; IBD, inflammatory bowel disease; IDA, iron deficiency anemia; GI, gastrointestinal; GERD, gastroesophageal reflux disease; HH, hiatus hernia; CD, celiac disease.

ment of IDA in other pathological conditions in gastroenterology are sparsely found in the literature.

Three pathological conditions that lead to the appearance of IDA are generally known, and they are blood loss, malabsorption, and chronic inflammation [4, 17–20]. There may be multiple combined mechanisms of anemia in the same patient. Gastroenterological diseases lead to anemia by their specific mechanisms due to bleeding

from polyps, tumors, or vascular malformations, inflammation in IBD, celiac disease (CD), or the presence of autoantibodies against intrinsic factor (pernicious anemia) [3, 21–23].

IDA has appropriate hematological characteristics. Among them are Hb values, which, according to the WHO definition, range below 130 g/L in men over 15 years of age, below 120 g/L in postmenopausal, and below 110 g/L in pregnant women [12]. Today, blood auto analyzers help to diagnose anemia as accurately as possible with additional tests, such as reduction of the mean corpuscular volume (MCV), hypochromia below 50 fL, reduced the mean corpuscular hemoglobin-below 12 pg in the presence of elevated red cells distribution width-values above 15.5 as well as low iron values-below 9 and low ferritin values-below 15 mg/L with normal C-reactive protein, and erythrocyte sedimentation rate values in the absence of inflammation [24, 25]. In case of low MCV (<80 fL), iron status should be checked by additional analyzes (serum iron, ferritin, transferrin, transferrin saturation, and total iron-binding capacity). On the other hand, despite the normal value of MCV, IDA cannot be ruled out, as is the case in chronic inflammatory GI diseases. The second most common anemia in gastroenterological patients is anemia of chronic diseases, where acute or chronic inflammation with immune activation is present [26]. The recommended first line of screening for CRC is the FOBT, which is widely applicable due to its noninvasiveness and diagnostic reliability [3, 27, 28]. In many GI diseases, anemia is the most crucial indication for endoscopy, and gastroenterologists must have a careful approach in the diagnostic algorithm depending on the clinical presentation and laboratory findings to make a diagnosis as soon as possible [1, 3].

Causes of IDA from the Upper GI Tract

Upper GI bleeding results from erosive or ulcerative changes, vascular lesions, or neoplasias up to Treitz ligament. The most common causes of upper GI bleeding are peptic ulcer disease, including the consequences of aspirin and nonsteroidal anti-inflammatory drugs use, variceal bleeding, Mallory-Weiss tear, and neoplasms of this region [6, 29]. Various diseases of the esophagus can cause IDA due to chronic inflammation, variceal, or nonvariceal bleeding. Gastroesophageal reflux disease symptoms can lead to mucosal lesions. Damage to the esophageal mucosa is possible due to usage of different drugs. Hiatus hernia (HH) often leads to mucosal damage, gastric reflux,

and esophagitis with intermittent mucosal defects. At the time of examination, erosion cannot always be detected, which does not exclude HH's etiological role in the existence of IDA [4]. Mechanical traumas of the gastric mucosa in HH are even visible (Cameroon lesions), and the cause of IDA is often determined [30]. Esophageal motility disorder is a rare cause of anemia, usually due to erosions. Nonvariceal esophageal diseases are not a common cause of IDA. Severe nonvariceal bleeding is possible in Mallory-Weiss syndrome. Esophageal ulcers are a rare cause of bleeding. Variceal hemorrhages in the liver cirrhosis are a major gastroenterological problem due to massive blood losses, followed by anemia, which most often require urgent care. The most severe disease of the esophagus that leads to anemia is cancer.

Bleeding from gastric ulcers can be of varying degrees, but gastroenterologists, in addition to drug therapy, solve it with sclerosing treatment, heat probes, or clips. In this way, bleeding can be successfully repaired. Further blood loss and more serious secondary anemia can be prevented, and the patient's recovery can be accelerated.

Gastric and duodenal ulcers are often clinically present with manifest bleeding but blood loss from these parts of the GI tract can sometimes be unrecognized until anemia occurs. This is undoubtedly due to nonsteroidal anti-inflammatory drugs frequent use, leading to a damage in the digestive tract, followed by overt or occult bleeding [31]. Sometimes a standard upper endoscopic examination will not reveal the cause of anemia in these patients, so small-bowel lesions caused by these drugs should be considered, and then an endoscopic video capsule may be useful [32]. Enteroscopy helps to find the cause of small-bowel bleeding. In that way, it was possible to detect polyps, diverticula, neoplasms, and angiodysplasia. In addition to bleeding from varicose veins, patients with liver cirrhosis may experience chronic blood loss due to portal hypertensive gastropathy and gastric antral vascular ectasia [33]. Gastric antral vascular ectasia, in addition to liver cirrhosis, can occur in some other chronic diseases, and it is believed that in this syndrome, portal hypertension is not etiologically associated with its occurrence [34]. The interventional gastroenterological approach in solving this problem involves primarily applying argon plasma coagulation.

Helicobacter pylori Infection and IDA

Several studies have linked the presence of *Helicobacter pylori* (HP) to chronic gastritis and IDA, and more than half of patients with unexplained IDA have a proven

HP infection [35]. Observational studies have linked HP to chronic gastritis and iron deficiency [9, 36]. However, the role of HP in the development of IDA has not been fully elucidated. Chronic HP gastritis is thought to lead to anemia through multiple mechanisms, from blood loss due to mucosal microdamage through decreased iron absorption to increased inflammatory cytokine and hepcidin levels with its known effects on iron metabolism [37, 38]. HP has been shown to increase hepcidin expression on the gastric mucosa [39], and hepcidin levels are decreased after successfully eradicating HP in IDA patients [3, 40]. Occult blood loss can result from erosive mucosal defects by infection of the altered mucosa. HP infection's significant role is also reflected in its role in developing ulcer disease and increasing gastric cancer risk. HP causes both atrophic gastritis and achlorhydria, which can lead to reduced absorption of iron. HP has been graded a class I carcinogen by the WHO because of its association with gastric adenocarcinoma [41, 42]. Meta-analyses provide additional evidence that HP eradication improves anemia and increases hemoglobin levels, especially in individuals with moderate to severe anemia [43–45]. The British Association of Gastroenterologists recommended testing and treating HP in patients with recurrent IDA and negative findings on upper and lower endoscopy [1, 9]. Maastricht V-Florence consensus claims that there is evidence linking HP to unexplained IDA, idiopathic thrombocytopenic purpura, and vitamin B12 deficiency. In these disorders, HP should be sought and eradicated [45]. The AGA suggests noninvasive testing for HP, followed by treatment if positive, over no testing [42].

Pernicious Anemia

Pernicious anemia occurs as a final stage of atrophic gastritis. It is characterized by megaloblastic anemia, achlorhydria, lack of intrinsic factor, and malabsorption of vitamin B12. There is also finding anti-parietal cell antibodies and antibodies against intrinsic factor with low values of serum pepsinogen I and II [46]. Observational studies indicate an increased risk of gastric adenocarcinoma and carcinoid tumors in patients with atrophic gastritis [9, 47].

Upper endoscopy and histological examination of biopsies reveal atrophy of the gastric mucosa, a precursor to dysplasia, and possible development of gastric cancer with an incidence of 0.27/100 persons per year [48]. It has been observed that in pernicious anemia, the risk of other malignancies increases [49]. The frequent cause of pernicious anemia is autoimmune atrophic gastritis. Besides that, au-

toimmune gastritis should be recognized as the nonbleeding cause of IDA [50]. IDA is among the earliest presentation of autoimmune gastritis as oxyntic gastric mucosal destruction, which leads to hypo- and achlorhydria, contributing to decreased iron absorption [51]. According to that, autoimmune gastritis is responsible for 20–30% of IDA refractory cases to iron replacement [35]. Additionally, IDA is a more frequent consequence of autoimmune gastritis in comparison to pernicious anemia. In line with that, autoimmune gastritis is frequently present as IDA in youngsters and the pernicious anemia in older patients [52].

Causes of IDA from the Lower GI Tract

Lower GI bleeding is a common cause of IDA and can originate from the small intestine or colon. The most common causes of blood loss from these anatomical regions are neoplasia, diverticular disease, angiodysplasia, IBD, and benign anorectal disorders [6, 29]. Colon diseases, the common causes of bleeding and anemia due to iron deficiency, are most often detected by colonoscopy. The reasons vary from once hard to recognize angiodysplasias to polyps and CRC. The risk of anemia in patients with CRC increases with tumors of larger diameter located on the right colon [53]. Anemia is usually hypochromic, less often of the mixed type. Anemia in CRC occurs in close to 50% of patients, and if they are asymptomatic, the diagnosis is often delayed [54]. Therefore, unexplained IDA is an important indication of GI tract malignancies [55]. Although malignant lesions of the GI tract, especially right colon cancer, were considered the most significant lesions found during endoscopy, cancers are detected in the entire GI tract. The most common causes of occult bleeding in IDA patients are inflammatory and ulcerative upper GI tract lesions [9, 56]. Diverticular disease is one of the most common causes of bleeding from the lower parts of the digestive tract, mostly in the elderly population [57]. Often, IDA can be a consequence of bleeding from angiodysplasia, responsible for 5% of GI bleeding. Recurrent bleeding from angiodysplasia is common, resulting in several localizations making their diagnosis and endoscopic resolution difficult [58].

Iron Deficiency Anemia in IBD

Anemia is the most common systemic complication and the extraintestinal manifestation of IBD [59–61]. It is usually anemia of chronic diseases due to iron deficiency

Fig. 1. Approach to IDA – diagnostic algorithm depending on the clinical presentation and laboratory findings. GI, gastrointestinal; IDA, iron deficiency anemia; Obs/Gyn, obstetrician/gynecologist.

and chronic inflammation [19]. The main mechanisms in this anemia are blood loss, malabsorption, and dietary restrictions. Its prevalence is more common in Crohn's disease than in ulcerative colitis [3, 62]. Inflammatory cytokines increase the production of hepcidin, which blocks ferroportin 1, resulting in IDA.

The frequency of anemia in these patients with a wide range of symptoms raises clinical suspicion in gastroenterologists that it could be IBD. Endoscopic findings, taking adequate biopsies, and histological analysis confirm the diagnosis of IBD. The ECCO guidelines recommend iron therapy to all patients with IBD and IDA to normalize Hb levels [62].

Celiac Disease

CD, a condition of the small intestine, is often the cause of anemia. It affects about 1% of the population and often remains undiagnosed [63]. The most common clinical manifestation of CD is IDA [64, 65]. IDA is mainly a consequence of iron deficiency and occurs in 80% of cases [66, 67]. Other mechanisms, especially deficiencies in folate and vitamin B12, participate in this anemia's pathogenesis due to malabsorption. Chronic inflammation mediated by inflammatory cytokines increase hepcidin's value, the primary regulator of iron metabolism with consequent anemia [68]. In about half of patients with CD who do not adhere to a gluten-free diet, the occult bleeding test is positive due to mucosal damage [69]. Also, iron absorp-

tion is significantly impaired due to villous atrophy [70]. A particular challenge is refractory IDA in patients who adhere to a gluten-free diet, and it requires extensive examination. CD should be considered because of its high prevalence in the IDA population, and, if suspected, CD serological screening should be performed by detection of IgA-anti-transglutaminase or IgG-anti-deamidated gliadin peptides antibodies [71]. Previous guidelines have advised routine small-bowel biopsies in patients regardless of CD serological tests [9, 72]. Although so far there is no clear evidence to suggest the need for routine small-bowel biopsies during upper endoscopy, many gastroenterologists opt for “screening” small-bowel biopsies during bidirectional endoscopy in the absence of other GI causes of IDA. However, the AGA suggests initial serological testing with small-bowel biopsies only in positive findings in asymptomatic patients with IDA [42].

Chronic Liver Diseases and IDA

Chronic liver diseases are most closely associated with IDA due to acute or chronic bleeding associated with portal hypertension and coagulation disorders. These are some of the reasons why 3-quarters of patients with chronic liver diseases are anemic [73]. IDA often accompanies the presence of esophageal varices, hematemesis, and melena in these patients. Blood replacement, iron, and emergency endoscopic procedures to stop bleeding are often necessary. Even in clinically silent nonalcoholic fatty liver disease, one-third of patients show sideropenia in laboratory tests [74].

Discussion

In everyday clinical practice, IDA is often seen, and its causes are usually diseases of the GI tract [75]. Blood loss from the GI tract is the most common cause of IDA in men and postmenopausal women [3, 76]. Despite many publications dealing with IDA, there is a lot of controversy in its evaluation approaches. Endoscopy is always indicated in individuals with IDA caused by occult GI bleeding, and views on the choice of endoscopic examination in HP, CD, and atrophic gastritis are not entirely consistent. Patients with GI symptoms should be evaluated based on their complaints. The presence of symptoms specific to a particular part of the GI tract may be a predictor of disease indicating the primary route of endoscope insertion, so there are recommendations that the

initial examination is directed to the site of specific symptoms [6] (Fig. 1). There are also views that, especially in the elderly with IDA in the absence of GI symptoms, the colon should be examined first. If the finding is negative, subsequent examination of the upper GI tract is advocated [6, 15].

A careful history is extensively used in planning a diagnosis because subtler symptoms are often overlooked by both the general practitioner and the gastroenterologist. There is no benefit from FOBT in IDA testing; it should not be advised to symptomatic IDA, overt bleeding, diarrhea, abdominal pain, or change in bowel habits, which only delays the necessary endoscopic examinations and leads to diagnostic delays [3, 77, 78]. These persons should be referred immediately for a gastroenterological examination. However, in patients with IDA in the absence of symptoms, the wide variability of pathologies and localization of possible causes in the GI tract and the most severe pathologies, especially malignancies that can lead to it, should be considered. According to British recommendations (BSG), upper and lower GI tract testing should be advised to all men and postmenopausal women with confirmed IDA free of other, non-GI visible blood loss [1]. US guidelines (AGA) recommend bidirectional endoscopy in asymptomatic postmenopausal women and men with IDA. This recommendation does not apply to patients with GI symptoms [42].

It is crucial not to accept the finding of esophagitis, peptic ulcer disease, or erosion as the cause of IDA until colonoscopy is performed [1]. Bidirectional endoscopy should be advised because of its diagnostic efficacy, time, and cost-benefit. In persons over 50 years and with a CRC family history, a colonoscopy should be recommended even in proven CD [1]. In patients with recurrent IDA and normal upper endoscopy and colonoscopic findings, HP should be eradicated if present. The AGA guide suggests noninvasive testing and treatment of HP, if positive [42]. The AGA suggests against the use of routine gastric biopsies to diagnose autoimmune atrophic gastritis in patients with IDA [42]. Due to malignancy risk, the European Society of Gastrointestinal Endoscopy guidelines recommend that endoscopic follow-up be considered every 3–5 years in these patients [79].

AGA advises initial serological testing in asymptomatic patients with IDA and small-bowel biopsy only positively regarding the CD. Therefore, any asymptomatic IDA raises CD suspicion; it is necessary to serologically test patients before referring them to a gastroenterologist. Further small-bowel examinations should be performed in case of inadequate response to iron therapy, especially

in need of transfusions [1, 10, 80]. The AGA guide advises asymptomatic patients with IDA and negative bidirectional endoscopy to first iron replacement therapy concerning routine small-bowel examination with a video capsule [42].

Video capsule endoscopy or enteroscopy may help diagnose angiodysplasia, Crohn's disease, and small-bowel neoplasia [1, 81, 82]. However, there is still a lot of ambiguity about the choice of adequate diagnostic criteria in patients with anemia, the type, sequence of endoscopic procedures, and whether noninvasive testing in specific conditions can be associated with anemia sufficient. There are also differing views on the necessity of routine gastric mucosal biopsies in HP infection or routine duodenal biopsies in CD detection. When planning the examination, gastroenterologists must consider the risks for certain diseases, especially malignant ones, following the patient's age. The benefit of endoscopic examinations is reflected in the high prevalence of GI malignancy in the IDA population, positively impacting treatment outcomes and the detection and optimal treatment of other nonmalignant diseases.

Conclusion

Anemia is widespread in many populations worldwide, and GI causes must be considered whenever the etiology is unclear. Investigating the causes of IDA presents a significant challenge for gastroenterologists due to the many pathological gastroenterology conditions that lead to it. Therefore, the gastroenterological approach in solving anemia's problem must be rational by the type of anemia and adjusted to the existing recommendations. Timely referral to a gastroenterologist and the optimal

diagnostic process reduces the risk of delays in diagnosis and provides efficient treatment, which is crucial for these patients' prognosis. GI malignancies are the most severe causes of IDA but the earlier detection of other benign diseases increases the chances of better outcomes. A gastroenterologist's task in solving anemia today is more accessible than in previous times, primarily due to the progress of endoscopy and advanced endoscopic procedures, which in many cases can make an accurate diagnosis and successfully repair a previously determined pathological condition.

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Conflict of Interest Statement

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Author Contributions

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