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Review Article

Acquired Refractory Iron Deficiency Anemia

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Abstract. Anemia is a global health problem affecting one-third of the world population, and half of the cases are due to iron deficiency (ID). Iron deficiency anemia (IDA) is the leading cause of disability in several countries. Although multiple mechanisms may coexist, ID and IDA causes can be classified as i) insufficient iron intake for the body requirement, ii) reduced absorption, and iii) blood losses. Oral iron represents the mainstay of IDA treatment. IDA is defined as "refractory" when the hematologic response after 4 to 6 weeks of treatment with oral iron (an increase of >=1 g/dL of Hb) is absent. The cause of iron-refractory anemia is usually acquired and frequently related to gastrointestinal pathologies, although a rare genetic form called iron-refractory iron deficiency anemia (IRIDA) exists. In some pathological circumstances, either genetic or acquired, hepcidin increases, limiting the absorption in the gut, remobilization, and recycling of iron, thereby reducing iron plasma levels. Indeed, conditions with high hepcidin levels are often under-recognized as iron refractory, leading to inappropriate and unsuccessful treatments. This review provides an overview of the iron refractory anemia underlying conditions, from gastrointestinal pathologies to hepcidin dysregulation and iatrogenic or provoked conditions, and the specific diagnostic and treatment approach.

Keywords: Iron deficiency; Iron refractory anemia; Malabsorption; Bleeding; Hepcidin; Intravenous iron.

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Introduction. Anemia is a global health problem affecting one-third of the world population, with half of the cases due to iron deficiency (ID).[1] The prevalence of iron deficiency without anemia remains elusive, although it has been estimated that it is at least double that of iron deficiency anemia (IDA). IDA itself is the leading cause of disability in several countries, with children and females of childbearing age being the most affected.[2] Moreover, ID is the cause of anemia in a significant proportion of elderly patients admitted to medical units.[3]

IDA is usually microcytic, defined as a decrease in mean red cell volume (MCV) due to reduced hemoglobin (Hb) production. However, in some circumstances, IDA can be normocytic if folate or vitamin B12 deficiencies coexist.

ID and IDA are the presenting signs and, in some cases, the sole of different medical conditions. ID and IDA causes can be classified as: i) insufficient iron intake

Table 1. Definitions related to iron deficiency.

Iron deficiency (ID)	Health-related condition in which iron availability is insufficient to meet the body's needs and which can be present with or without anemia.[85]
Iron deficiency anemia (IDA)	Depressed levels of total body iron in the presence of anemia.
Iron refractory anemia	Absence of hematologic response (an increase of >= 1 g of hemoglobin) after 4 to 6 weeks of treatment with oral iron.
Iron-refractory iron deficiency anemia (IRIDA)	Iron-deficiency anemia unresponsive to oral iron treatment, referring to the genetic disease caused by a mutation in TMPRSS6, the gene encoding transmembrane protease, serine 6, also known as matriptase-2.

for the body requirement, ii) reduced absorption, and iii) blood losses, although multiple mechanisms may coexist. Age, sex, clinical history, and symptoms are essential in guiding the diagnostic work-up for the identification of the underlying cause.[4] Oral iron represents the mainstay of IDA treatment. IDA is defined as "refractory" when the hematologic response after 4 to 6 weeks of treatment with oral iron (an increase of >= 1 g/dL of Hb)[5] is absent. The underlying cause of iron-refractory anemia is usually acquired and frequently related to gastrointestinal (GI) pathologies, although a rare genetic form called iron-refractory iron deficiency anemia (IRIDA) exists (See definitions reported in **table 1**).

Iron absorption is limited to 1 to 2 mg daily, while most of the iron needed is provided through recycling by macrophages that phagocytize senescent erythrocytes. The two latter mechanisms are controlled by the hormone hepcidin, the master regulator of iron homeostasis.[6] Hepcidin is a peptide primarily produced by the liver,[7] which regulates the systemic flux of iron by modulating ferroportin levels through its degradation.[8] Ferroportin is highly expressed in duodenal enterocytes to transport the iron absorbed with the diet, in hepatocytes to transport stored iron, and macrophages to transport recycled iron. Hepcidin expression is regulated by several mechanisms, including iron status, erythropoietic stimuli, and inflammation. In ID, hepcidin synthesis is suppressed to facilitate the absorption of iron.

However, in some pathological circumstances, either genetic or acquired, hepcidin increases, reducing surface ferroportin, limiting the absorption, remobilization, and recycling of iron, thereby reducing iron plasma levels.[8] Indeed, conditions with high hepcidin levels are often under-recognized as iron refractory, leading to inappropriate and unsuccessful treatments. This review provides an overview of the iron-refractory anemia underlying conditions (**Figure 1**), from GI pathologies to hepcidin dysregulation and iatrogenic or provoked conditions.

Autoimmune Atrophic Gastritis. Chronic atrophic gastritis (CAG) is defined as a loss of gastric glands replaced by pseudo-pyloric or intestinal metaplasia or fibrosis, causing impaired gastric acid secretion (hypochlorhydria/achlorhydria) and intrinsic factor deficiency. Historically, two main types of CAG have been documented: type A and type B chronic atrophic gastritis. Type A is associated with autoimmune etiology, anti-parietal cell antibodies (APCA), and corpus involvement with the antrum sparing. On the other hand, type B is usually associated with environmental factors such as Helicobacter Pylori (HP) infection and generally affects antral mucosa.[9]

However, more recent consensus and guidelines have revised the terminology, regrouping CAG by considering morphology, topography, distribution of gastritis, and the possible coexistence of multiple etiologies. Asides from classical dichotomous classification, it is now assumed that histological sampling can hint at unclassified damage to the gastric mucosa, and multiple patterns of gastritis can be found in the same patient. Moreover, an overlap between different types of gastritis (e.g., H. Pylori corpus predominant pattern) has been described in some patients.[10,11] Chronic atrophic gastritis prevalence changes extensively among epidemiological studies as different diagnosis and definition criteria are adopted. However, a systematic review esteems a prevalence of CAG as high as 23.9% in the general population and up to 27% in selected groups when serological criteria, such as pepsinogen I or pepsinogen I/pepsinogen II ratio, are adopted.[12]

Patients with CAG are usually affected by a certain degree of anemia. Vice versa, some studies show that up to 20-27% with refractory IDA are diagnosed with autoimmune gastritis.[13,14] Nonetheless, the burden and clinical effects of CAG are relatively underestimated by GI specialists.[15]

As HP infection is examined separately in this review, henceforth, we will discuss autoimmune chronic atrophic gastritis and its relationship with IDA. According to the literature, roughly 2% of the general population is affected by autoimmune atrophic gastritis (AAG). This illness is usually found in females over 60 years old with related autoimmune diseases.[16] Once established, AAG can be responsible for many pathologic alterations involving multiple apparatuses (e.g., gastrointestinal, hematological, neurological). As AAG affects oxyntic gland production of hydrochloric acid and intrinsic factor, both B12 and iron deficiency anemia are reported in these patients. An acidic environment is essential for the reduction, solubilization, and absorption of iron and intrinsic factor, a well-known element for the assimilation of cobalamin. In this subset of patients, current evidence shows that IDA usually occurs before

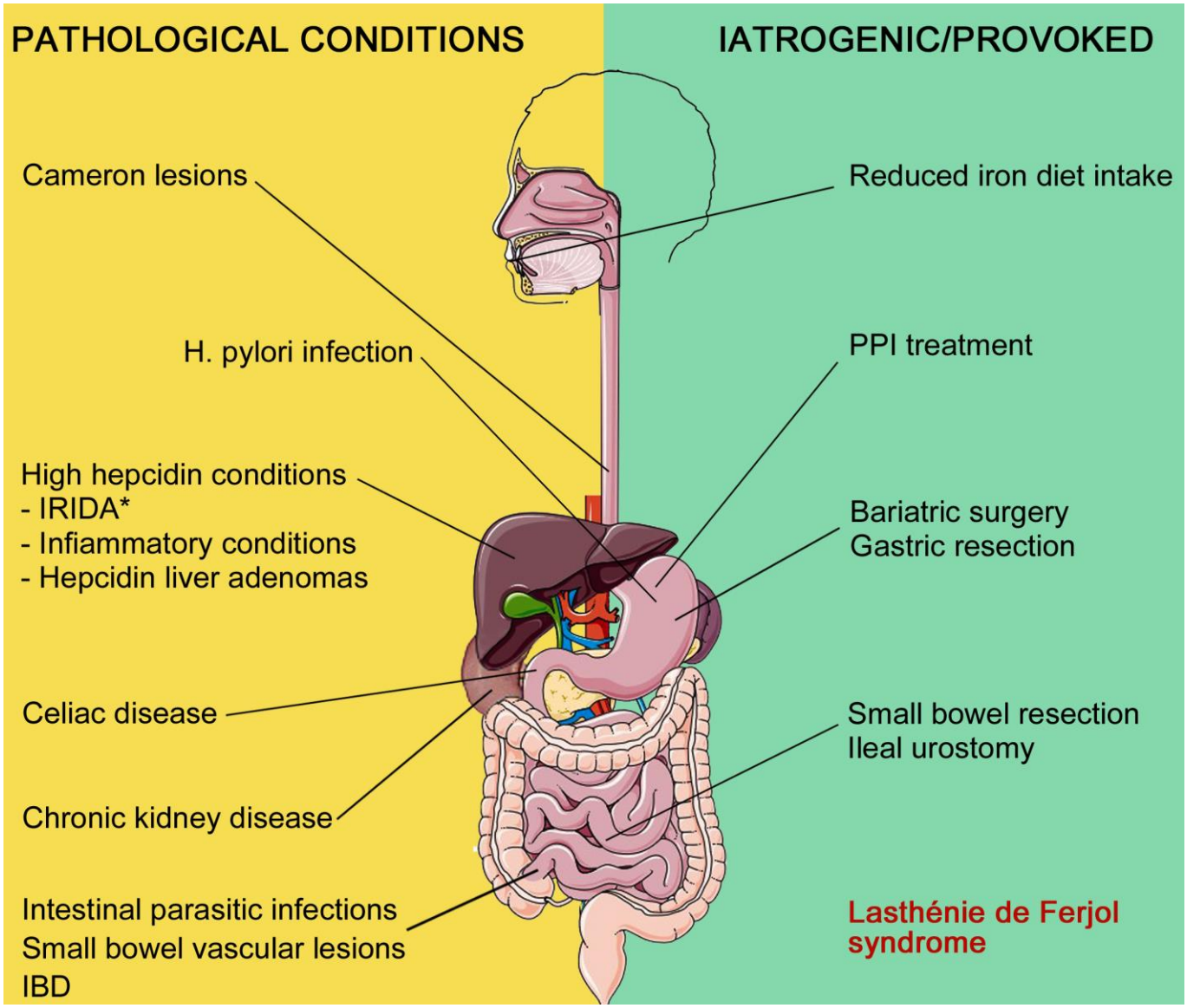

Figure 1. Causes of iron refractory iron deficiency anemia. IRIDA: Iron refractory iron deficiency anemia; IBD: Inflammatory bowel diseases.

B12 deficiency. It has also been observed that IDA can be the only sign of AAG at clinical presentation in up to 53% of cases. However, subtle alterations, such as anisocytosis, could hint at an early stage of the disease and should always be considered when evaluating a patient.

Patients with AAG-associated IDA are usually younger (up to 20 years) and female. This occurs probably because the reserves of Vitamin B12 can last for a fair amount of time before macrocytic anemia shows up. Overlapping menstrual losses that worsen iron deficiency could explain why premenopausal women account for a more significant percentage of AAG-associated IDA. On the contrary, older male patients with AAG are often diagnosed with B12 deficiency anemia, probably due to a long-lasting unidentified disease. Some studies report dimorphic anemia as a consequence of both iron and B12 deficiency affecting erythrocyte development.

Several studies showed that AAG could be the only cause for iron-refractory anemia. Thus, when examining a patient with IDA who does not respond well to oral iron supplementation, a thorough interrogation on upper gastrointestinal disturbances is mandatory. These patients are often affected by several unspecific symptoms such as abdominal bloating, pain, and nausea. Sometimes symptoms such as early satiety, postprandial fullness, and epigastric pain are also reported, giving rise to differential diagnosis between other common gastrointestinal diseases (e.g., functional disorders, celiac disease).

Nonetheless, patients without enteric symptoms should also be suspected of gastrointestinal involvement.

Besides, attention should be given to those patients with IDA affected by other autoimmune diseases classically related to AAG (e.g., diabetes mellitus type 1, autoimmune thyroiditis).[13,14,16,17]

To our current knowledge, the mainstays for AAG

diagnosis are endoscopic gastric evaluation and mucosal biopsies taken following the Sydney Houston protocol.

This protocol allows a correct gastric evaluation and detects 90% of intestinal metaplasia when attained. APCA and anti-intrinsic factor antibodies (AIFA) were once considered a mainstay of the diagnosis. However, current guidelines report a relatively low sensitivity for AIFA, low specificity for APCA, and an overall low diagnostic accuracy when serological markers are considered alone. The best practice imposes accurate histological examination, whereas the serological test may help in corroborating the diagnosis.[13,17,18] Recent laboratory-based scores taking into account gastrin, hemoglobin, and mean cell volume levels have been proposed for identifying subjects more likely to be affected by AAG. Notably, when proton-pump inhibitor (PPI) use and Zollinger-Ellison syndrome have been excluded, gastrin alone stands out as a good indicator of AAG in the atrophic stage, and markedly elevated levels are associated with type 1 neuroendocrine tumor.[19,20]

Helicobacter Pylori. The relationship between Helicobacter pylori and IDA has always been debated. Chronic gastritis resulting in hypochlorhydria overlapping AAG, occult blood loss due to chronic erosive gastritis and peptic ulcers, reduced ascorbic acid, subsequent intestinal iron absorption, and iron sequestration and utilization by the pathogen itself are the supposed mechanisms for IDA in HP infection.[21] The 2017 Maastricht V/Florence Consensus Report declares that HP association with IDA has been conclusively proven in the adult and pediatric population, thus recommending HP eradication in patients with moderate to severe anemia with negative bidirectional endoscopy.[22] However, the authors stated that the overall level of evidence is very low, and the recommendation grade is weak. Notably, this statement is mainly based on relatively old meta-analyses and multicenter studies. Similarly, the American College of Gastroenterology 2017 Guidelines suggest that patients with unexplained IDA despite an appropriate evaluation should be tested for HP infection. Treatment should be given to those who tested positive. However, there are multiple concerns over HP testing (low positive predicting value in low prevalence scenarios) and extensive treatment.[22,23] Furthermore, thanks to the broader availability of capsule endoscopy, it is no longer generally recommended to stop endoscopic examinations after a negative bidirectional endoscopy and encourage to look for other bleeding sources throughout the small GI.[24]

Moreover, a recent retrospective single cohort study based on many consecutive patients undergoing esophagogastroduodenoscopy and standard testing for HP infection excluded an association with IDA in univariate and multiple logistic regression analyses.[25]

When approaching a patient with IDA at the current state of the art, HP should be regarded as a possible cause, but it should not prevent further examinations. We recommend ruling out more frequent causes of IDA while planning patient follow-up and dismissal.

Celiac Disease. Celiac disease (CeD) is an autoimmune enteropathy triggered by gluten in genetically predisposed subjects carrying HLA DQ2 or DQ8 genes. The duodenum and the proximal small bowel (jejunum) are the gastrointestinal tracts mostly affected by mucosal inflammation.[26] Eventually, mucosal inflammation ends in mucosal atrophy and villa blunting when left untreated, causing nutrients malabsorption.

Anemia and CeD are strictly related since the absorption of these nutrients is necessary for red cell production. Elemental iron and heme compounds are absorbed exactly in the gastrointestinal mucosal area involved in CeD.[17,27]

Several studies and a meta-analysis showed that anemia affects up to 69% of patients diagnosed with CeD, especially adult females. Moreover, up to 4% of patients affected by anemia are diagnosed with CeD if an active serological screening strategy is pursued.[28,29]

Notably, since iron is absorbed in the duodenum, IDA is the most common extra-intestinal sign of CeD. Also, IDA could be the main and only manifestation in relatively asymptomatic celiac patients.[30]

Recent studies showed that there is indeed a relationship between the degree of villous atrophy and iron serological markers. Consequently, severe anemia cases are associated with severe histological patterns of CeD (Marsh-Oberhuber 3b and 3c). Besides, it has been demonstrated that iron regulatory proteins expressed by the enterocyte (e.g., divalent metal transporter 1 DMT1, hephaestin, ferroportin 1 FP1, Transferrin receptor 1 TfR1, and Duodenal cytochrome B Dcytb) are regularly present in CeD, thus denying a possible impaired iron mechanism disorder in this subset of patients.[31,32] Currently, malabsorption is believed to be the primary pathogenic mechanism for IDA in CeD; other genetic factors (e.g., polymorphisms or mutations in TMPRSS6) could worsen the clinical scenario.[33]

For the reasons mentioned above, CeD should always be considered when evaluating a patient with IDA, especially if the patient is young and complains of gastrointestinal symptoms (dyspepsia, bloating, diarrhea, constipation).

Current guidelines suggest this active case-finding policy in patients affected with unexplained IDA or iron refractory IDA.[34-36]

Life-long Gluten-Free Diet (GFD) is the mandatory and most effective treatment for this specific type of IDA. However, in the persistence of IDA or slow repletion of iron storage during GFD, iron supplementation could be needed. This clinical scenario is typically related to higher iron demands in premenopausal women or slow

normalization of villous atrophy. In adult patients, this last process could last longer than three years.[37]

Surgical Procedures. Several surgical procedures may lead to ID due to malabsorption. ID is well documented in bariatric surgery, but other surgical procedures can be involved. With the growing prevalence of obesity worldwide, bariatric surgery will be more frequent, given its more significant and sustained improvement in weight loss than non-surgical treatments. Good results on weight also have their side effects, including the risk of nutritional deficiency, with ID as one of the most relevant. According to recent data,[38] postoperatively, iron deficiency prevalence varies between 18 and 53 % after Roux-en-Y gastric bypass and between 1 and 54 % after sleeve gastrectomy. The prevalence of ID is also proportional to the follow-up length, and it is higher in premenopausal women.[39,40]

Different factors contribute to iron deficiency development after surgery: the pre-existing predisposition related to obesity itself, since obesity-induced systemic inflammation may increase hepcidin levels and contribute to ID; the iron intake becomes inadequate to major requirement due to a higher blood volume.[41,42]

Several studies proved a reduced iron intake after bariatric surgery, primarily due to increased satiety and reduced appetite with a reduction of micronutrient intake,[43] together with a lower tolerance for red meat[38] and poor adherence to dietary indications and recommended supplementations.[44] The digestion and absorption of iron are also affected by the induced alteration in gastrointestinal anatomy and physiology, leading to the reduction of the area involved in iron absorption and reduced hydrochloric acid secretion (essential for the reduction of the ferric ion into its ferrous absorbable form).

Other types of surgery, with various indications, may lead to IDA. These include gastric resection, procedures involving the first tract of the small intestine, and proctocolectomy. A frequent complication in patients undergoing surgery for ulcerative colitis is pouchitis, which is associated with IDA (6-21% of patients with functional pouches) due to mucosal bleeding and impaired iron absorption.[45]

Considering urological surgery, procedures that lead to excluding a bowel segment from the GI may cause metabolic and nutritional disturbances. Folic acid and vitamin B12 deficiency have been described, while the importance of ID is debated: Bambach and Hill described a "frequently found ID after major resection of the small intestine (100±330 cm)",[46] while Salomon et al. did not found any evidence of metabolic disorders, including iron deficiency, after an extended follow-up after Camey type I ileal enterocystoplasty, considering this result possibly related to the short ileal length (35 cm) used in the Camey type I operation.[47] A more recent study, in a population of children and adolescents that underwent ileal urostomy, revealed a reduced level of serum iron and increased total iron-binding capacity (TIBC) in the long term follow up in a small proportion of patients, suggesting as "prudent" to investigate iron parameters in these patients.[48]

Occult Blood Losses.

Diaphragmatic hernia and esophagitis. Gastric bleeding from Cameron lesions (linear gastric ulcers or erosions on the mucosal folds at the diaphragmatic impression) is a documented cause of IDA in large diaphragmatic or hiatus hernia;[49,50] however, also axial and para-esophageal hernia, in the absence of Cameron lesions, have been related to IDA.[51] IDA reported incidence for all types of hernia varies from 8% to 42% in different cohorts, with an average of 20%.[52] The presence of hiatal hernia itself, independently of esophagitis, has been shown to increase IDA risk.[53] The hypothesis for these forms of IDA has been related to mechanical trauma plus esophagitis, and erosions, or gastroesophageal acid reflux. Of note, the absence of endoscopically detectable erosions does not exclude their causal role in most patients with hernia-related IDA. Considering the treatment of hernia and esophagitis, surgery, in combination with PPI, did not show better results compared to PPI therapy alone in treating and preventing the recurrence of IDA, even in the case of larger diaphragmatic hernia.[51,52]

Small bowel vascular lesions. Small bowel bleedings account for approximately 5% of all cases of GI bleeding[54] and consist of the majority of obscure gastrointestinal bleeding (OGIB), defined as GI bleeding from an unidentified origin that persists despite a comprehensive upper and lower GI evaluation.[97] Age of onset and detailed medical history, including information on comorbidities, is essential for determining small bowel bleeding origin.

The American College of Gastroenterology guidelines in 2015 included inflammatory bowel disease, Dieulafoy's lesion, neoplasia, Meckel's diverticulum, and polyposis syndromes among the most common causes in subjects under the age of 40, while angioectasia, Dieulafoy's lesion, neoplasia, and non-steroidal anti-inflammatory drugs ulcers in those over the age of 40.[55] Also, rare conditions can cause small bowel bleedings.

Capsule endoscopy (CE) is the first-line diagnostic tool for patients with IDA and suspected obscure midgut bleeding, while device-assisted enteroscopy should be performed as the second-line intervention and in case of operative enteroscopy or bioptic sampling.[30]

Intestinal parasitic infections. Several studies have shown parasitic infections, especially *T. trichiura* and

hookworm infections, to be strongly associated with IDA. Hookworm infections are associated with mucosal damage and endogenous loss of iron, while *T. trichiura* and *E. histolytica* cause bleeding and dysentery by invading the mucosa of the large intestine. Given these mechanisms, parasitic infections need to be considered in the presence of IDA, especially if iron -refractory.[56-58]

Drug-Related Iron Refractory Anemia. Hypo- or achlorhydria induced by proton pump inhibitors increase the risk of ID and IDA. A recent population-based case-control study in the United Kingdom showed that continuous use of PPI for one year or longer increased the risk of ID compared to the non-exposed subjects or patients treated for less than one year.[59] Suboptimal response to oral iron treatment in patients with ID receiving a PPI has been documented.[60] Several studies demonstrate that PPIs are overprescribed; thus, more attention is required to evaluate benefit and risk balance.

Self-Induced Bleeding. Lasthénie de Ferjol syndrome (LF) is a rare psychiatric disease, affecting women mainly. It is characterized by severe recurrent IDA caused by repeated episodes of self-induced blood-letting. The microcytic anemia observed in a patient with LF syndrome is non-specific, reflecting only chronic blood loss. The work-up is negative for gastrointestinal or gynecological bleeding and nutritional deficiencies.

Anemia improves with therapy, but patients almost inevitably interrupt the treatment with the reappraisal of blood-letting sessions. Despite severe debilitation, most LF syndrome patients continue to fulfill their professional and social duties; they appear highly cooperative and willingly submit to even the most invasive diagnostic procedures to discover the actual cause of their symptoms. The diagnosis is based on the findings of anemia, together with a unique psychological history. Early diagnosis is usually difficult, but it may prevent repeated hospitalizations and the risks associated with invasive diagnostic procedures; management is usually challenging but should be based on long-term psychotherapy.[61,62]

Iron Refractory Anemia and Hepcidin Dysregulation. High hepcidin levels induce ferroportin degradation, limiting the absorption of iron in the gut and the recycling from the liver and macrophages in the spleen.

Iron-refractory iron deficiency anemia (IRIDA). Iron refractory iron deficiency anemia (IRIDA) is a rare hereditary recessive form of microcytic hypochromic anemia. It is caused by mutations in the transmembrane protease serine 6 (*TMPRSS6*) gene, encoding for matriptase-2, which lead to inappropriately high hepcidin expression for the low iron status and restricted intestinal iron absorption.[63] Patients present with low transferrin saturation and variable values of serum ferritin. Diagnosis is made through molecular analysis, usually during childhood. The disease is refractory to oral iron treatment but shows a slow response to intravenous iron injections with partial correction of the anemia.[64]

Anemia of chronic disease. Elevated hepcidin levels are among the hallmarks of anemia of inflammation (AI), also known as anemia of chronic disease (ACD). It is estimated that up to 40% of all the anemia cases can be considered AI or with significant AI contribution, accounting for 1 billion affected individuals.[2] Under conditions of chronic inflammation, increased expression of interleukin-6 (IL-6) results in the activation of transcription 3 (STAT3)-mediated hepcidin expression and, consequently, limited dietary iron absorption and availability for erythropoiesis.[65,66] AI is usually mild to moderate normochromic and normocytic. Characteristically, AI has reduced circulating iron concentrations and transferrin saturation (TSAT) and reduced reticulocyte count. Serum ferritin can be normal or increased, depending on the underlying condition.[67]

Inflammatory bowel diseases. Anemia is the most common extra-intestinal complication in inflammatory bowel diseases (IBD), with a reported prevalence higher than 70%.[68] The etiology of anemia in IBD is multifactorial, mostly involving ID and chronic inflammation.[68] IDA, the main cause of anemia in these patients, is due to chronic blood loss in the gastrointestinal tract, reduced iron intake, and malabsorption. AI is mediated by inflammatory cytokines, including tumor necrosis factor-α, interleukin-1, IL-6, interleukin-10, and interferon-γ.[69,70] Indeed, hepcidin has been demonstrated to be high in IBD patients.[71-73] Hepcidin levels may vary according to the disease activity and the opposite contribution of inflammatory activity versus iron deficiency.

Chronic kidney disease. Hepcidin is cleared by the kidney, where it is mainly reabsorbed and degraded by the proximal tubular mechanism that metabolizes other peptides. In chronic kidney disease (CKD), iron metabolism is disrupted because of high hepcidin concentrations.[74] Several mechanisms contribute to high hepcidin levels and include the inflammatory pathogenesis of kidney disorder, decreased clearance, and hemodialysis or peritoneal dialysis-related complications.[75,76] In these patients, ID is a consequence of decreased iron absorption and increased iron losses, mostly from gastrointestinal bleeding[77] but also from iatrogenic effects. Indeed, hemodialysis causes blood loss due to residual blood in the dialysis equipment, anticoagulation, and frequent laboratory examinations.[74]

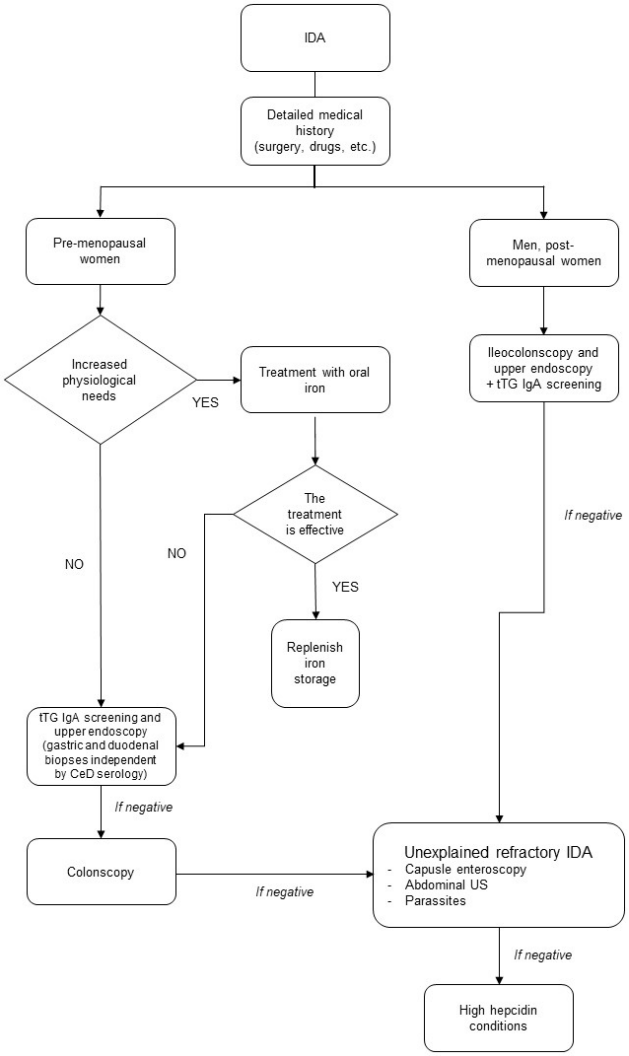

Figure 2. Approach to IDA and unexplained refractory IDA. tTG: tissue transglutaminase; CeD: celiac disease; US: ultrasound.

Hepcidin adenomas. A form of microcytic hypochromic iron deficiency anemia, refractory to oral treatment, was described in a cohort of patients affected by type 1a glycogen storage disease (GSD1a), a rare recessive disorder due to deficiency of glucose-6 phosphatase, which catalyzes a reaction involved in both glycogenolysis and gluconeogenesis. This condition is characterized by hypoglycemia, and current treatment leads to prolonged survival of affected subjects up to adulthood, with the development of several complications, including liver adenomas. The observation of IDA correction after adenomas resection led to further studies that showed inappropriately high expression of hepcidin mRNA in adenoma tissue (while hepcidin suppression was documented in the normal liver tissue). The aberrant high-level hepcidin mRNA expression is supposed to play a direct role in anemia pathogenesis, which presents the same characteristics of IRIDA.[78,79]

Diagnostic Approach. Considering the refractory IDA definition, we will focus on specific requirements after the IDA first-line approach has been performed (**Figure 2**). It can be complicated and even experienced, and trained physicians may be misled by low compliance and factitious anemia. C-reactive protein and other acute-phase markers need to be assessed, together with kidney function; coexisting cobalamin or other vitamin deficiency can help address the diagnosis.

Medical and pharmacological history needs to be re-evaluated, focusing on GI symptoms and the use of PPI or other drugs that can impair gastric acidity; occult blood losses can be induced by drugs or by hereditary

Table 2. Characteristics, indications, and side effects of oral and IV iron formulation.

Oral iron agent		**Fe (mg)**	**Dosage**	**Drug/Supplement**	**Side Effects**
Ferrous sulphate	*Ferro-Grad; Tardyfer*	80-105 mg Fe^{2+}	1 tab/day	Drug	• Nausea • Vomit • Epigastric discomfort • Constipation / diarrhea • Metallic taste • Dark colored stools
Ferrous gluconate	*ferroComplex*	80 mg Fe^{2+}	1 tab/day	Drug	
Na+ ferrigluconate	*Ferlixit*	62,5 mg Fe^{3+}	1 fl/day	Drug	
Fe-glycine sulphate	*Niferex*	100 mg Fe^{2+}	1 tab/day	Drug	
Fe-bisglycinate	*Ferridol*	30 mg Fe^{2+}	1 -3 tab/day	Supplement	
Sucrosomial iron	*SiderAl*	14 mg	1 tab/day	Supplement	
IV iron agent		**Fe (mg)**	**Dosage**	**Total replacement dose (single infusion)**	**Side Effects**
Na+ ferrigluconate	*Ferlixit*	62,5 mg Fe^{3+}	1 fl/day diluted in SS	NO (repeated access needed)	• Nausea • Vomit • Pruritus • Headache and flushing • Myalgia and arthralgia • Back and chest pain (resolution within 48 h)
Fe-sucrose	*Venofer*	100 mg	50 – 200 mg diluted in SS	NO (repeated access needed)	
Fe-carboxymaltose	*Ferinject*	100 – 500 mg Fe^{3+} (50 mg/ml)	500 – 1500 mg (1000 mg *maximum single dose*) diluted in SS	YES	
Ferric derisomaltose/ Fe-isomaltoside	*Monofer*	100 – 1000 mg (100 mg/ml)	maximum single dose 20 mg/kg diluted in SS	YES	
Ferumoxytol	*Feraheme*	510 mg Fe^{3+}	510 mg diluted in SS	YES/NO (510 mg x 2 recommended dose)	

SS: saline solution

Table 3. Diagnostic work-up and treatment of specific conditions causing iron refractory anemia.

Condition	Specific diagnostic work-up	Specific treatment approach
Autoimmune atrophic gastritis	- Cobalamin - Serum gastrin; APCA; anti-intrinsic factor antibodies - Endoscopy with biopsies	- oral iron supplementation is an effective first-line treatment in patients with mild anemia (limited intestinal daily absorption could prevent a correct restoration of iron reserves).[26,29,86] - IV iron is required only by a few patients. IDA might take more time to recover than B12 deficiency.[26,27,30] No specific recommendations are now available to supplement nutrients other than vitamin D, iron, and vitamin B12.[26,29]
Helicobacter pylori	- Hp fecal antigen - Urease breath test (no if on PPI treatment) - Endoscopy with biopsies (optional)	- Oral iron is the first-line treatment, together with Hp eradication therapy. H. pylori eradication is associated with a more rapid response to oral iron therapy as compared with the use of iron therapy alone. It also leads to enhanced iron absorption even in subjects who do not receive oral iron therapy.[87]
Celiac disease	- tTG IgA antibodies (and total IgA) - Duodenal biopsy, HLA screening for DQ2 or DQ8 genotypes	- Oral iron supplementation is first-line treatment: the standard of care is iron sulfate, which can be associated with low tolerance due to gastrointestinal side effects such as nausea, epigastric pain, diarrhea.[88] Sucrosomial iron and an iron compound based on alginic acid and ferrous bisglycinate are both effective in celiac patients.[89] If IDA is non-responsive to oral iron treatment in the setting of CeD, another cause for anemia and refractory celiac disease must be suspected.[90] Folate deficiency and copper deficiency may be subtle clinical conditions that could muddle clinical evaluation.[30,91]
Bariatric surgery		- Oral supplementation is a first-choice treatment (ASMBS guidelines)[92]. It should be taken in divided doses separately from calcium supplements, acid-reducing medications, and foods high in phytates or polyphenols (Grade D, BEL 3). - If the ID does not respond to oral therapy, IV iron infusion should be administered (Grade C, BEL 3). Various studies compared oral iron formulation, and a recent RCT has compared the oral treatment to IV ferric carboxymaltose with good results in terms of efficacy and recurrence of ID even if with higher costs.
IRIDA	- Suggestive history and clinical assessment - Sequencing of the TMPRSS6 gene	- oral iron is generally ineffective (few cases of partial response to sustained oral supplementation are described) - IV iron administration leads to partial and slower correction of anemia Hb levels rarely normalize, and microcytosis and reduced TSAT persist, while ferritin levels can be normal or even increased after iron treatment.[64]
Chronic kidney disease		- oral iron supplementation is recommended in patients with IDA not receiving erythropoietic stimulating agents (ESAs) and not on hemodialysis.[93] - IV iron should be proposed to subjects under ESAs treatment and/or on hemodialysis. A recent meta-analysis also supports the increased use of IV iron for patients with CKD stages 3 to 5. Among patients undergoing hemodialysis, a high-dose intravenous iron regimen administered proactively was superior to a low-dose regimen administered reactively and resulted in lower doses of ESAs.[94]
Inflammatory bowel diseases		- IV iron is recommended as first-line treatment in patients with clinically active IBD, with previous intolerance to oral iron, with hemoglobin below 10g/dL, and in patients who need erythropoiesis-stimulating agents.[95] - oral iron is effective in patients with IBD and may be used in patients with mild anemia, whose disease is clinically inactive, and who have not been previously intolerant to oral iron. No more than 100mg elemental iron per day is recommended in patients with IBD.[95] A recent Cochrane review concludes that IV ferric carboxymaltose probably leads to more people having resolution of IDA than IV iron sucrose. Oral ferric maltol may lead to more people having resolution of IDA than placebo. They were unable to draw conclusions on which of the other treatments is most effective in IDA with IBD due to the low number of studies in each comparison area and clinical heterogeneity within the studies. Overall, IV iron delivery probably leads to a greater response in patients compared with oral iron.[96]

APCA: anti-parietal antibodies; IV: intravenous; IDA: iron deficiency anemia; PPI: proton pump inhibitor; tTG: tissue transglutaminase; HLA: human leukocyte antigen; CeD: celiac disease; ASMBS: American Society for Metabolic & Bariatric Surgery; RCT: randomized clinical trial; ID iron deficiency; IRIDA: iron refractory iron deficiency anemia; Hb: hemoglobin; TSAT: transferrin saturation; CKD: chronic kidney disease; ESAs: erythropoiesis-stimulating agents; IBD: inflammatory bowel diseases

bleeding disorders. History of travel or other risk factors for parasitic infection has to be considered.

The probability of HP infection is higher in men and postmenopausal women, while refractory IDA stating during childhood can be found in IRIDA patients. A specific approach for each condition is reported in **Table 3**.

Treatment. The basis of IDA treatment is the administration of iron to restore the deposits and induce Hb production, together with the removal of the causes, whenever possible. The mainstay is oral iron administration, which should be prolonged for at least three months to replete iron stores and normalize ferritin levels. Oral iron is cheap and does not require hospital access. However, it is associated with frequent side effects, especially GI symptoms that often lead to treatment interruption.[80] It has been recently shown that oral alternate-day administration can have fewer gastrointestinal side effects and reduced hepcidin levels than conventional daily dosage, ameliorating iron absorption and improving patient tolerability.[81,82] Thus, in oral treatment failure, low adherence should be suspected, but iron refractoriness causes should also be considered.

Iron can also be administered intravenously (IV), with more rapid and effective correction of ID and IDA bypassing iron absorption. It has higher costs, but with more recent formulation, such as ferric carboximaltose, fewer/single-dose administration is often sufficient, with shorter time for anemia correction and reduced hospital accesses. New IV iron formulations, compared to those available in the past, are safe and exhibit a low immunogenic potential.[83] The cost-benefit ratio favors IV supplementation, as indicated by the European Medicines Agency (EMEA: http://www.emea.europe.eudocument WC500150771, 2013).

Characteristics, indications, and side effects of oral and IV formulation are reported in **Table 2**. The choice between different formulations is mainly based on Hb values, IDA etiology, comorbidities, and oral formulation tolerance.

The specific treatment approach for each condition is presented in **Table 3**.

Conclusions. IDA is a highly prevalent disorder affecting all ages. However, it remains under-recognized, and unique definitions of ID, anemia, and IDA are necessary to reach a proper diagnosis.[84] Once diagnosed, IDA requires appropriate diagnostic work-up to identify the underlying cause and start the proper treatment. Oral iron refractory conditions require specialist management and specific treatment to avoid the worsening of IDA and consequences on the patient's quality of life.

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