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Case Report

Revisiting Anemia at Older Age

Rodolfo Delfini Cancado[1,2*]

[1]Faculty of Medical Sciences of Santa Casa de São Paulo, São Paulo (SP), Brazil

[2]Hospital Samaritano-Higienópolis, São Paulo (SP), Brazil

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***Corresponding author:** Dr. Rodolfo Delfini Cancado, Rua Havai, 440, CEP: 01259-000, São Paulo SP, Brazil, E-mail: rodolfo.cancado@gmail.com

A B S T R A C T

Anemia affects a significant number of the elderly population, representing a worldwide public health problem that is predicted to increase further in the coming years because of the demographic drive. Being typically mild, it is falsely perceived as a minor problem, particularly in the elderly with multimorbidity, so that it often remains unrecognized and untreated. Anemia in the elderly (AE) is independently associated with mortality and loss of physical function in older people and is generally multifactorial. Anemia of inflammation, iron deficiency (ID), cobalamin deficiency, and renal insufficiency are the most common causes of AE. The proportion of unexplained anemia is consistently declining due to recent advances highlighting the role of several conditions, including clonal hematopoiesis, "inflammaging," treatable androgen deficiency in men, and under-recognized (ID). We review AE's leading clinical and pathophysiological aspects, giving practical insights into managing the treatment of ID, including oral iron and IV iron. The cause and severity of anemia, comorbidities, the time remaining until delivery, and the patient's wishes are essencial factors that must be considered when deciding the therapeutic approach.

Keywords: Anemia; Iron deficiency; Anemia of inflammation; Older adult

1. Introduction And Contextualization

Population aging has occurred rapidly in developed countries since the beginning of the 20th century. Since the 1960s in Brazil, it has brought one of the biggest challenges to contemporary public health[1-3]. According to the World Health Organization (WHO), it is estimated that the number of people over 60 will increase from 900 million (12% of the population) in 2015 to 2 billion (22% of the population) in 2050 (http://www.who.int/mediacentre/ factsheets/fs404/en/).

Two epidemiological phenomena were decisive for this demographic transition: the reduction in mortality and the progressive decline in fertility in the second half of the last century. This rapid and progressive increase in the number of adults and older adults was responsible for the change in the profile of diseases in the world, or epidemiological transition, with chronic health conditions predominating[4].

In general, the presence of at least one chronic condition occurs in more than 80% of older age, and at least 40% of these individuals present multiple diseases simultaneously (multimorbidity). The most significant impact of chronic conditions on the health of older adults is the functional impairment in carrying out their daily activities. In this sense, health should no longer or cannot be measured by the presence or absence of diseases but rather by the degree of preservation of functional capacity, thus determining successful or unsuccessful aging[1,2].

2. Anemia: Definition

Anemia is the hematological alteration most commonly found in medical practice. It is defined as a sign or manifestation of an underlying disease, not a clinical entity. This means that anemia does not represent a definitive diagnosis but rather a laboratory finding that demands careful diagnostic investigation

– a detailed clinical history and physical examination, followed by appropriate laboratory tests. This practice allows, in most cases, the correct diagnosis of the cause of anemia, therefore appropriate treatment[5,6].

For more than two decades, several clinical studies have drawn attention to the importance of anemia as an independent factor in a worse prognosis for the patient as well as a worse prognosis for the disease. That is, it is associated with higher rates of morbidity and mortality, worse quality of life, and worse results in clinical, surgical, chemotherapy, and radiotherapy treatment. Therefore, it is an actual pathological condition, often treatable, and should not be seen simply as an abnormal laboratory parameter[5-7].

From a pathophysiological point of view, the state of anemia is due to a reduction in the number of red blood cells or the concentration of circulating hemoglobin (Hb), which, regardless of its cause, determines a decrease in tissue oxygenation resulting from a reduced oxygen transport capacity to tissues. According to the criteria proposed by the WHO, anemia is laboratory defined as Hb less than 13 g/dl for men and 12 g/dl for women[8].

Anemia in the Elderly (AE): clinical implications and leading causes

According to the WHO, the prevalence of AE is 23.9%, and this rate increases with age (it can reach 60% in people over 80 years old) and with the presence of comorbidities such as diabetes, heart failure, cardiovascular disease, inflammatory and neoplastic diseases. In this way, AE is considered a public health problem[1,6,8].

The existence of anemia is a sign of a more severe outcome in relation to any disease and can result in the following significant issues for the patient:

• diminished physical, emotional, cognitive, and mental well-being

• decreased immune function and thermal regulation

• heightened hospitalization and morbidity

• increased mortality.

2.2 Main Causes of Anemia in the Elderly

AE generally has multiple underlying causes and is often associated with more than one predisposing factor[1,8,9]. The leading causes of AE are listed in (**Table 1**).

Table 1: Leading causes of anemia in the elderly.

Parâmetro	Prevalência
Anemia of inflammation	30-60%
Iron Deficiency	15-30%
Vitamina B_{12}/Folato deficiency	15-20%
Renal insuficiency	8-12%
Unknown cause	20-30%

2.3 Anemia of Inflammation

Anemia of Inflammation (AI) is a clinical condition characterized by the development of anemia in patients with inflammatory, neoplastic diseases, infectious diseases. The peculiar aspect of this syndrome is the presence of anemia associated with a decrease in serum iron concentration and transferrin saturation index and, paradoxically, normal or increased serum ferritin and medullary iron levels. AI is the most common cause of anemia in hospitalized patients, particularly when analyzing patients over 65 years of age and the second most common cause of anemia, after iron deficiency anemia (IDA). The main clinical entities associated with AI are rheumatoid arthritis, Crohn's disease, chronic kidney disease, heart failure, infection, inflammation, cancer, trauma, and surgery[1,6,8-10].

The three main mechanisms involved in the etiopathogenesis of AI are:

• decreased red blood cell survival,

• inadequate erythropoietic response to anemia associated with inappropriately low secretion of erythropoietin and reduced iron supply to the bone marrow, resulting in the inability of the bone marrow to increase its erythropoietic activity sufficiently to compensate for the reduced survival of red blood cells,

• Iron metabolism disorder is undoubtedly the most important mechanism. This disorder is characterized by an increased synthesis of pro-inflammatory cytokines (IL-1, IL-6, and of alpha tumor necrosis), increased hepcidin synthesis, reduced autophagy secondary to increased NF-κB,. These factors can lead to an increased inflammasome response and a pro-inflammatory state, also known as inflammatory aging and increased reactive oxygen species that can lead to increased inflammasome response.

Tipically, AI exhibits is a mild to moderate in intensity (Hb between 9 and 12 g/dl, rarely failing below less than eight 8 g/dl). Red blood cells are typically normochromic and normocytic, although in 30% of cases they may be hypochromic and microcytic. The reticulocyte count is generally normal or slightly elevated, and may be inadequately increased given the severity of the anemia.[5,8,10-12].

Serum ferritin concentration is normal or increased. However, as AI is considered an inflammatory state (acute or chronic), ferritin, as an acute phase protein, can present normal or elevated values, which do not truly express the amount of iron in the body. Therefore, these patients may present ID with normal or elevated ferritin values[5,8,10-12].

It is important to remember that there is no other cause of low ferritin (< 30 ng/mL) than iron deficiency; however, the reverse is invalid. Ferritin values between 30 and 300 ng/mL should be interpreted cautiously in an inflammatory, infectious, or neoplastic state because they may hide the associated iron deficiency. A detailed clinical history, physical examination, and CRP measurement greatly help in these clinical situations[5,8,10-12].

2.4 Iron Deficiency Anemia (IDA)

The primary cause of iron deficiency is the imbalance between the amount absorbed and consumption and losses, which occur through several pathways, resulting in a reduction in total body iron, with depletion of stores and some degree of tissue deficiency. Iron deficiency generally results from a combination of two or more factors (Table 2)[1,5-9].

Androgen deficiency is a plausible cofactor of unexplained AI, especially in older men.70 A recent randomized, placebo-controlled study including older men with low testosterone levels (<275ng/dL) and mild anemia (Hb > 10g/dL) observed that administration of testosterone gel (1%) for 12 months was more effective in correcting anemia than placebo (in 58% versus 22% of cases, respectively; p=0.002). A possible explanation for the increase in Hb with the use of testosterone is that testosterone suppress the production of hepcidin and, thus, subsequently, increase the absorption and mobilization of iron for erythropoiesis[13,14].

Vitamin D deficiency, often seen in the older adults, increases the risk of anemia. Possible mechanisms proposed for

this association are modulation of pro-inflammatory cytokines, lower bone marrow response to the action of erythropoietin, and modulation of hepcidin levels[13,14].

ID in the elderly is often multifactorial and overlooked. Serum ferritin is the most reliable marker of ID. Ferritin levels tend to increase in older people due to a pro-inflammatory state associated with aging and comorbidities, predominantly renal and heart failure(**Table 2**)[5,8,10-12].

Table 2: Main causes of Iron Deficiency[1,5-9].

Increased iron requeriment	Excessive loss of iron (Blood loss)
Growth* Menstruation** Pregnancy*** Lactation ESA therapy	Gastrointestinal bleeding Esophageal: varicose veins, carcinoma, ulceration, reflux esophagitis Gastric: polyp, cancer, ulcer, gastritis, angiodysplasia, telangiectasia, antral gastric vascular ectasia, associated with the use of aspirin, non-steroidal anti-inflammatory drugs, anticoagulants, antiplatelet agents Small intestine: inflammatory bowel disease, duodenal ulcer, Ancylostoma duodenale and Necator americanus infection, cancer, polyp, angiodysplasia, telangiectasia, Meckel's diverticulum, associated with intense exercise, milk allergy Large intestine: cancer, polyp, diverticular disease, angiodysplasia, inflammatory bowel disease, Heyde's syndrome# Anus: Hemorrhoid Entire gastrointestinal tract: hereditary hemorrhagic telangiectasia Gynecological bleeding: abnormal uterine bleeding##; uterine cancer or other cancers of the reproductive tract, intrauterine device Urinary bleeding: cancer: kidney, bladder, prostate Intravascular hemolysis: PNH, gait hemoglobinuria, thrombotic microangiopathy, gait hemoglobinuria, malaria Respiratory bleeding: Hemoptysis (cancer, infection) Blood donation Exercise Excessive iatrogenic blood loss###
Inadequate dietary intake and/or defective absorption of iron	
Low bioavailability of Fe diet@ Vegetarian or vegan practice Inflammatory bowel disease Celiac disease Parasitosis Obesity Post-gastroplasty (gastric bypass) Post-gastrectomy Atrophic gastritis Helicobacter pylori infection Medications: antacids, proton pump inhibitors, calcium, tannin IRIDA@@	

ESA, erythropoiesis-stimulating agents; *during early childhood and adolescence; ** physiological blood loss exceeding daily iron intake; *** additional iron requirement for each pregnancy of approximately 1000 mg for expansion of maternal erythrocyte mass and placental and fetal development; @resulting from poverty, especially in low-income countries, early cessation of breastfeeding, inadequate transition diet;@@ IRIDA, iron-refractory iron deficiency anemia caused by mutations in the TMPRSS6 gene; #Heyde's syndrome (severe aortic stenosis, syndrome type 2 acquired von Willebrand disease, angiodysplasia and ECD); ##abnormal uterine bleeding usually related to uterine fibroid, adenomyosis, endometrial hyperplasia or dysfunctional uterine hemorrhage fibroid; exacerbated by bleeding disorders (von Willebrand disease, hemophilia A or B and platelet dysfunction); PNH, paroxysmal nocturnal hemoglobinuria; ###excessive blood collection for diagnostic tests and iron losses during hemodialysis.

The laboratory tests and their respective results for the differential diagnosis between AI, iron deficiency (ID), and IDA are presented in (**Table 3**)[1,5-12]. The reticulocyte hemoglobin (RetHe) content indicates the amount of iron available for incorporation into the young red blood cells in the bone marrow in real time. It has been used as an important biomarker in the differential diagnosis between AI and IDA[5,8,10-12].

Table 3: Differential diagnosis of types of iron deficiency[1-5,12]

Parameter	**ID**	**IDA**	**AI**	**IDA + AI**
Symptoms	Asymptomatic or mild symptoms of anemia	Mild-severe symptoms of anemia	Symptoms of the underlying disease, symptoms of anemia	Symptoms of the underlying disease, symptoms of anemia
Hemoglobin	Nl /↓	↓	↓	↓
MCV	Nl /↓	↓	Nl/↓	↓
TSAT	20-45%	< 20%	< 20%	< 20%
Ferritin, ng/mL	< 30	< 30	NL/↑	NL/↑
Reticulated hemoglobin content	↓	↓	↓	↓
Hepcidin	Nl/↓	↓	↑	Nl /↓

ID, iron deficiency; IDA, iron deficiency anemia; AI, anemia of inflammation

2.5 Current recommendations regarding treatment with oral iron

Iron is a vital element for proper function in the human body, playing a central role in cellular energy metabolism. However, the body has no mechanism to increase iron excretion, which can lead to excess iron. To protect against this, the absorption rate of iron is low, typically between 3% and 30%, due to the action of hepcidin in the duodenal enterocytes. Therefore, much of the supplemental iron ingested is not absorbed and is responsible for the high rates of gastrointestinal adverse events (AEs), such as nausea, vomiting, diarrhea, constipation, metallic taste, especially with supplements containing iron in the ferrous form[5,15-17].

Studies have shown that a single dose of 100-200mg can increase serum hepcidin, which remains elevated for 24 hours before returning to baseline within 48 hours. The higher the dailydose of iron, the more significant the increase in serum hepcidin level and, consequently, the lower the absorption rate the following day. In an effort to improve tolerance and adherence to oral iron, the current recommendations for treating ID with oral iron are presented in (**Table 4**)[8-10,15-17].

Table 4: Current recommendation for the treatment of iron deficiency with oral iron[8-10,15-17].

Current recommendation for the treatment of iron deficiency with oral iron

- A single daily dose of oral iron is preferable to divided doses because divided doses twice or three times a day are physiologically ineffective.
- Ferrous salts should be taken 1h before meals, between meals, or before bedtime (the time of greatest gastric acid production)
- Ferric salts can be given during or after a meal.
- The major problem with oral iron supplements is that 20-56% of patients cannot tolerate them because of GI AEs, including abdominal distress, nausea, vomiting, constipation, diarrhea, metallic taste, and dark stool; and the discontinuation of treatment is up to 20%.
- It is important for prescribers to inform patients of these potential ADs before commencing oral iron therapy and to encourage an open dialogue so that should negative effects occur, alternative therapies can be provided.
- The common practice of administering ferrous salts with food in an attempt to alleviate GI AEs can effectively decrease absorption by 40% to 66%.
- AE rates related to oral iron are dose-dependent. It is important for the physician to be aware of the amount of elemental iron present in different medications, as this varies considerably according to the compound used or available.
- Doses up to 100 mg of elemental iron should be prescribed once a day. Doses > 100 mg – 200 mg of elemental iron, should be prescribed on an alternate-day regimen to optimize iron absorption, reduce the rate of GI AEs, and improve treatment tolerance. The rate of iron absorption is 40%-50% greater on alternate days versus consecutive days for doses between >100 and 200 mg of elemental iron.
- Avoid daily dose of elemental iron > 200 mg
- With consistent oral iron supplementation, reticulocytosis starts in 4 to 5 days, and Hb begins to improve by the second week. The main criteria for a good response to treatment is an increase of at least 2 g/dL is expected after 3-4 weeks of treatment.
- As an overarching principle, with any IDA patient, provide enough iron to not only correct the Hb deficit, but enough to provide measurable storage iron as reflected by the SF. The SF can then be monitored for ongoing iron losses and prevent ID and IDA with appropriate administration of supplemental iron.
- Oral iron therapy is often required for at least 3 to 6 months, depending on the intensity of the ID, continuity of blood loss, occurrence of AEs and, consequently, adherence to treatment. The goal of iron replacement is not only to correct the Hb deficit but to provide enough iron to replete iron stores and normalize ferritin levels (serum ferritin > 30 ng/mL and TSAT > 20%).
- Periodic monitoring (SF and TSAT) and retreatment prior to the recurrence of ID are recommended among high-risk populations: pregnant women (at the first prenatal visit and in each trimester during pregnancy) and among specific groups of nonpregnant women of childbearing age.
- There are no biochemical markers to predict the likelihood of response to oral iron. In addition to the problem of AEs, impaired iron absorption such as inflammatory bowel disease and other malabsorption states, prior gastric bypass surgery, and concomitant administration of drugs can inhibit iron absorption can decrease responsiveness to oral iron.
- Intake of citrus fruits containing vitamin C (orange, lemon, acerola) before or during a meal increases iron absorption. Multivitamins containing divalent metals (zinc, copper, manganese) and various dietary components (phytates, polyphenols, calcium and phosphates) reduce the absorption of ferrous salt. Therefore, it is recommended that they be administered separately from other vitamin supplements.

Comparison between the four main iron supplements marketed in Brazil

Variable	Ferrous sulphate	Ferric Salts		
		Ferrocarbonyl	Aminochelated Iron	Ferripolymaltose
Administration	Preferably with an empty stomach*	During or after meal		
High	Efficiency	Intermediate to high		
High (35-55%)	Rate of Adverse events	Intermediate (15-35%) to Low (10-15%)		
Treatment tolerance	Low	Intermediate to high		
Quantity of elemental iron	20%	30%	20%	33%

Definition of treatment failure with oral iron:
Hb ≤ 2 g/dL after 3 to 4 weeks of treatment with 100 to 200 mg of elemental iron/day.

Most frequent causes of treatment failure with oral iron:

- Continuing blood loss due to failure to identify bleeding and/or iron absorption disorder.
- Medication inappropriately used - poor adherence to treatment due to gastrointestinal AEs and/or inadequate dose and/or insufficient duration.
- Coexisting disease interfering with the response (reducing iron absorption and/or favoring bleeding) to oral iron treatment - chronic kidney disease associated inflammatory or infectious disease.
- Diseases associated with iron absorption disorder - celiac disease, autoimmune atrophic gastritis and Helicobacter pylori infection; incorrect diagnosis.
- Combined nutritional deficiencies.

2.6 Current recommendations regarding treatment with intravenous iron

The preferred route for treating ID with iron is ora due to its effectiveness and low cost. However, in situations of intolerance to oral iron or failure of response (for example, continued blood loss, post-gastroplasty, concomitant disease interfering with the response (chronic kidney disease, associated inflammatory or infectious disease, celiac disease, autoimmune atrophic gastritis, and Helicobacter pylori infection), treatment with intravenous iron should be considered[18-26].

The objective of treatment is to correct anemia and normalize iron stores, that is, to achieve serum ferritin levels greater than 30 ng/ml. To this end, it is recommended that the response to treatment be assessed using blood counts, serum iron levels, total iron binding capacity, and ferritin after six weeks of administration of the full dose of iron calculated for the patient. Regardless of the product used, it is recommended that IV iron be applied in a hospital environment or, preferably, in clinics or infusion units by nursing professionals with experience in applying IV medications and with medical supervision. The current recommendations for treating iron deficiency with IV iron are available in (**Table 5**)[18-29].

2.7 Megaloblastic anemia due to vitamin B12 (Cobalamin) deficiency

Megaloblastic anemia (MA) is a group of conditions characterized by delayed maturation of the nucleus of hematopoietic cells resulting from insufficient DNA synthesis due to blockage of the conversion of uridine monophosphate to thymidine monophosphate. MA's main aspect is ineffective erythropoiesis, the intramedullary destruction of erythropoietic precursors. The same phenomenon also occurs in the granulocytic and megakaryocytic series, which justifies, in addition to anemia, the presence of leukopenia and thrombocytopenia[30,31].

Table 5: The current recommendation for the treatment of iron deficiency with IV iron[18-29].

Main indications for IV iron treatment

- Oral iron intolerance determined by the occurrence of AEs.
- Unsatisfactory response with oral iron due to intestinal absorption disorder associated with conditions such as: gastric bypass, gastrectomy, chronic gastrointestinal inflammatory disease (H. pylori infection, Celiac disease, Crohn's disease, ulcerative colitis and atrophic gastritis).
- Recurrent bleeding (gastrointestinal, gynecological) in which the amount of iron absorbed orally is not sufficient to meet the demand resulting from excessive iron loss.
- Rapid iron replacement in order to reduce transfusion requirement in patients with IDA scheduled for medium to major elective surgery, including childbirth and the puerperium.
- Faster normalization of iron stores avoiding prolonged use of oral therapy and its AEs.
- Patients with non-dialytic chronic kidney disease with serum ferritin < 100 ng/mL or on hemodialysis with serum ferritin < 200 ng/mL in order to ensure and optimize the response to erythropoietin administration.
- Special situations such as: pre-deposit autotransfusion programs, religious issues (Jehovah's Witness patients)

Goals of IV iron treatment

- Faster correction of anemia (an increase of 2 to 3 g/dL of Hb after 4 weeks of treatment) and iron stores
- Reduce/eliminate the need for blood transfusions
- Optimize the use of erythropoietin (cancer, chronic kidney disease)

Main practical guidelines for the use of IV ferric saccharate

- To calculate the total dose in mg of iron to be replaced, the Ganzoni formula can be used: body weight (kg) x (target Hb – current Hb) x 2,4 + 500.
- There is no need to perform a test dose before application.
- Dilute the compound only in 0.9% saline solution (SF). Do not dilute in glucose solution.
- Dilute each ampoule (5 mL, 100 mg) in at least 100 mL of saline solution.
- For each solution containing 100 mg of ferric saccharate, the infusion time should be at least 15 minutes. Therefore, the infusion of the solution containing 200 mL (or more) of SS and 200 mg of ferric saccharate should be done within 30 to 60 minutes.
- It is important to respect the drug infusion time.
- Respect the interval between applications, which is at least 24 hours.
- Respect the maximum dose limit per application, which is 200 mg (2 ampoules) and the maximum weekly dose, which is 600 mg.

Main practical guidelines for the use of IV ferric carboxymaltose

Ferric carboxymaltose (FCM) has been available for over a decade and is indicated for the treatment of IDA in various clinical situations. It is an innovative iron complex composed of a core of ferric hydroxide surrounded by a layer of carbohydrate (maltose) that combines the advantages of iron dextran (high stability) with the advantages of ferric saccharate (low immunogenicity). After administration, FCM is phagocytosed by macrophages, especially in the bone marrow, maltose is degraded and iron molecules are released to form the intracellular pool of iron in the form of ferritin or destined for erythropoiesis via plasma transferrin. Another important advantage of this product is its convenient dosage, that is, FCM can be administered in high doses (dose of up to 1000 mg of iron or maximum dose of 15 mg/kg per application) IV in at least 15 minutes and without the need for a test dose.

Hemoglobin (g/dL)	Total dose of ferric carboxymaltose	
	Body weight >35 e <70 Kg	Body weight ≥70 Kg
< 10	1500 mg	2000 mg
≥ 10	1000 mg	1500 mg

- There is no need to perform a test dose before the first infusion.
- Dilute the compound only in 0.9% saline solution (SF), 50-100 mL and 200 mL for 500 mg and 1000 mg of FCM, respectively. Do not dilute in glucose solution.
- Dilute each ampoule (10 mL, 500 mg) in at least 100 mL of saline solution.
- The recommended minimum infusion rate is 100 mg/min. Infusion time is, at least, 6 minutes for up to 500 mg and 15 minutes for doses between >500 mg and 1000 mg.
- The maximum dose per application should not exceed 1000 mg (>15 mg/kg body weight) of iron per application.
- Doses > 15 mg/Kg should be divided into 2 infusions 7 days apart Do not administer more than 1000 mg of FCM per week. Therefore, the interval between 2 or 3 applications of 1000 mg is at least 7 days.
- FCM is for IV use only and should not be administered subcutaneously or intramuscularly.
- Ferinject® 100 mg/mL solution for infusion (5 mL or 10 mL vial)

Main practical guidelines for the use of IV ferric derisomaltose

Ferric derisomaltose (FD) is available in Europe and has recently been licensed in the US, Australia and Brazil. Like FCM, it is an innovative iron complex composed of a core of ferric hydroxide surrounded by a layer of carbohydrate (maltose) that combines the advantages of iron dextran (high stability) with the advantages of ferric saccharate (low immunogenicity); it can be administered in high doses (maximum allowed dose of 20 mg of iron/Kg of body weight). If the total iron dose calculated is > 20 mg/Kg/weight, the supplementary dose should be performed after ≥ 7 days.

Hemoglobin (g/dL)	Total dose of ferric derisomaltose	
	Body weight <70 Kg	Body weight ≥70 Kg
≥ 10 e < 12	1500 mg	2000 mg
< 10	1000 mg	1500 mg

- Whenever possible, administer the total dose in the 1st infusion as long as it does not exceed the maximum allowed dose (> 20 mg of iron/kg of body weight)
- If total dose > 20 mg/Kg/weight: 2nd dose after ≥ 7 days.
- Dilution ≥ 1 mg/ml for stability reasons. For a 500 mg dose, dilute 100 mL in saline solution and infuse the solution in at least 15 minutes. For doses ≥1000 mg, dilute 200 mL in saline solution and infuse the solution over at least 30 minutes.
- Monofer® solution for infusion of 100 mg/mL in packaging containing 1 vial of 5 mL or 10 mL.

Contraindications to the use of IV iron

- Any type of anemia unrelated to iron deficiency.
- TSAT > 45%
- Serum ferritin ≥ 500 ng/mL, regardless of TSAT value.
- Patients with acute infection, especially in the presence of bacteremia/septicemia
- Patients with known hypersensitivity to iron or any component of its formulation

Warnings and recommendations with IV iron
• The use of IV iron should be done with caution in patients with asthma, eczema or atopic allergies, especially in those with a past history of moderate to severe hypersensitivity reactions, including anaphylactic reactions. In these cases, the use of antiallergic drugs (IV diphenhydramide) and/or corticosteroid therapy (IV hydrocortisone) as premedication is recommended. • Due precautions must be taken to avoid venous extravasation during drug administration, which can cause local changes such as: pain, irritation and browning of the skin. If this occurs, administration of the product must be stopped immediately. • The use of IV iron should be avoided in patients with severe hepatic impairment. • The use of IV iron should be avoided in pregnant women ≤ 13 weeks of gestation • To date, FCM and FD are not recommended in children or adolescents (< 18 years) • IV oral should not be administered concomitantly with oral iron • Regardless of the product used, it is recommended that IV iron be applied in a hospital environment or, preferably, in clinics or infusion units with experience in IV drug administration, by duly trained nursing professionals with medical supervision. • Observation of the patient for at least 30 minutes after the end of IV iron infusion is recommended.
When and how to assess response to IV iron treatment
It is recommended to carry out complete blood count, reticulocytes, serum iron, total binding capacity of iron and ferritin after 4-6 weeks of administration of the total dose of iron calculated for the patient.
IV iron safety profile
• Minor reactions (eg, headache, symptomatic hypotension, back pain, heartburn, chest tightness, dyspnea, nausea, tachycardia, rash, and vomiting) are due to labile free iron and consist of pressure in the chest or back or facial flushing – symptoms not seen with severe hypersensitivity. Further, premedication with antihistamines can cause somnolence, diaphoresis, tachycardia, and hypotension which may be attributed to the intravenous iron. Intervention with antihistamines or vasopressors can convert these minor reactions, which usually resolve in minutes without therapy, into hemodynamically significant AEs, ostensibly due to the intravenous iron. • FCM has a lower risk of hypersensitivity, but a higher incidence of hypophosphatemia, which in most cases is not severe, is temporary and asymptomatic. • Although very rare, severe hypersensitivity reaction can occur with IV iron

The prototype of MA is pernicious anemia characterized by a deficiency of vitamin B12 (cobalamin) resulting from the lack of intrinsic factor, necessary for its absorption, and common in Older individuals[30,31].

The main causes of vitamin B12 deficiency are:

- gastric atrophy
- autoimmune diseases (vitiligo, Hashimoto's thyroiditis)
- Helicobacter pylori infection
- gastroplasty, gastrectomy, intestinal resection
- medications (long-term use of antacids, proton pump inhibitors, biguanides [metformin])
- alcoholic beverage

Patients with MA typically experience a slow onset of anemia, which can intensify to produce symptoms like weakness, palpitation, dyspnea, and neurocognitive dysfunction. Mild jaundice can cause the skin to take on a lemon-yellow hue due to associated pallor. Atrophy of the lingual papillae can result in a smooth, red tongue. Vitamin B12, acting as a cofactor in the synthesis of methionine and tetrahydrofolate, is essential for 5-adenosylmethionine production, which is necessary for the methylation of phospholipids in the myelin sheath. Patients with MA commonly experience subacute combined degeneration of the spinal cord, peripheral polyneuropathy, optic neuropathy, and neuropsychiatric changes as the main neurological manifestations.[30,31]

Cobalamin deficiency can cause drowsiness, perversion of taste and smell, worsening of visual acuity; memory loss, confusion, personality change, paresthesia, ataxia, dementia or psychosis, impotence, urinary and fecal incontinence, convulsions, choreiform, and athetoid movements. On physical examination, it is common to find neurological changes such as Romberg's sign, ataxic gait, abolition of kinetic-postural sensitivity, abolition of vibratory sensitivity, paresthesia sensation in the hands, and atrophy of the optic nerve[30-32].

In most cases, the first suspicion of the diagnosis of MA is usually the finding of increased MCV (> 100 fl,), regardless of the presence or absence of anemia. There are other conditions that cause macrocytosis in addition to MA, including myelodysplastic syndrome, multiple myeloma, aplastic anemia, pregnancy, excessive alcohol use, liver disease, hypothyroidism, and reticulocytosis secondary to hemolysis or hemorrhage[33-34].

The changes in peripheral blood and bone marrow resulting from a lack of folic acid and vitamin B12 are indistinguishable (megaloblastosis), but only vitamin B12 deficiency can cause neurological severe changes, sometimes irreversible, even before the onset of anemia[33,34].

2.8 Anemia of Unknown Cause

The main situations of anemia of unknown cause or not fully understood, and require further investigation includes:

- Unexplained anemia
- Myelodysplastic Syndrome
- Idiopathic/clonal cytopenia of undetermined significance
- Clonal hematopoiesis of undetermined potential (CHIP)

Myelodysplastic syndrome (MDS) is a group of clonal hematopoietic disorders that tend to occur more frequently in the elderly, with a median age at diagnosis of 65 years or older. In fact, isolated anemia is often the first clinical manifestation of low-risk MDS. However, many suspected cases require further testing, such as bone marrow evaluation with biopsy, immunohistochemistry, myelogram, immunophenotyping, karyotyping, flow cytometry, and molecular studies[20,22,35].

It is estimated that up to 30% of anemias with an unknown cause are related to low-risk MDS. It is important to remember that, anemia can be treated with treatment with erythropoietin or with new agents that inhibit the beta superfamily of erythropoiesis transforming growth factor (luspatercept) Studies have shown that these treatments can help correct anemia effectively.[35-41].

ERecent findings suggest that age-related changes in the hematopoietic system, such as a decline in blood cell production, alterations in chemokine and cytokine production, and changes in the bone marrow microenvironment, can be attributed to the selection of mutant hematopoietic stem clones. Clonal hematopoiesis of undetermined potential (CHIP) can be identified through peripheral leukocyte tests that reveal somatic mutations in key genes like DNMT3A, TET2, and ASXL1, which are also associated with hematological malignancies. These mutations

are present in nearly 10% of healthy individuals over the age of 70, and their prevalence increases with age. Studies of elderly individuals with unexplained cytopenias suggest that clonal hematopoiesis may be the underlying cause, particularly in cases where there is anemia and a single clonal mutation (known as idiopathic/clonal cytopenia of undetermined significance), but not all diagnostic criteria for MDS is met.[20,22,35-41].

Final Considerations

Older people, even mild anemia is clinically significant, indicating some level of impairment or health decline and an increased susceptibility to severe adverse outcomes, such as mortality. Iron deficiency is the primary cause of anemia in older individuals, and its assessment through clinical and laboratory investigation, and endoscopic investigation when needed and feasible, is highly valuable. Properly treating anemia in older adults enhances their quality of life and can mitigate morbidity and mortality.

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