Review Article

Clinical management of iron deficiency anemia in adults: Systemic review on advances in diagnosis and treatment

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ABSTRACT

Global burden disease studies point out that one of the top cause-specific anemias is iron deficiency (ID). Recent advances in knowledge of iron homeostasis have shown that fragile patients are a new target population in which the correction of ID might impact their morbidity, mortality and quality of life. We did a systematic review using specific search strategy, carried out the review of PubMed database, Cochrane Database of systemic reviews and international guidelines on diagnosis and clinical management of ID from 2010 to 2016. The International guidelines were limited to those with peer–review process and published in journal present in citation index database. The eligible studies show that serum ferritin and transferrin saturation are the key tests in early decision-making process to identify iron deficiency anemia (IDA). The clinician has to carefully consider fragile and high-risk subset of patients such as elders or individuals with chronic diseases (i.e chronic kidney disease, inflammatory bowel disease, chronic heart failure). Treatment is based on iron supplementation. Infusion route should be preferentially considered in frail patients especially in the view of new iron available formulations. The available evidences indicate that (i) recurrent IDA should always be investigated, considering uncommon causes; (ii) IDA might worse the performance and the clinical outcome of fragile and high-risk patients and require an intensive treatment.

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1. Background

Studies of global burden diseases (GBD 2010) have pointed out that anemia is a growing problem of public health also in well-developed Countries [1,2]. In both sexes, the main causes of anemia identified by GBD are iron deficient anemias (IDA), thalassemias, sickle cell disease and infection related anemias, such as malaria, schistosomiasis or hoockwarm [1,2]. IDA and β-thalassemias are the top two cause-specific anemia burden and both of them are characterized by microcytosis. By excluding inherited red cells disorders, iron deficiency (ID) seems to be the main cause of increased years life lived with disability (YLD) observed in all ages and in both sex by GBD 2010 studies. This results in low patient quality of life (QoL) and increase risk of developing severe organ complications with growing cost for National health systems [3]. Furthermore, IDA affects a large part of adult and elderly patients admitted to Internal Medicine Units. The precocious and correct identification of the cause(s) underlying IDA as well as the specific

therapeutic intervention are crucial to impact YLD and patients QoL. Here, we review the advances in pathogenesis, diagnosis, treatment and areas of uncertainty in IDA in adults from January 2010 to December 2016.

2. Methods

The present panel of Authors, using specific search strategy, carried out the review of PubMed database, Cochrane Database of systemic reviews and international guidelines on diagnosis and clinical management of ID from 2010 to 2016. The International guidelines were limited to those with peer–review process and published in journal present in citation index database. The main following search terms were used: microcytic anemia, iron deficiency, iron deficiency anemia, occult bleeding, nutritional deficiency diagnosis, treatment(s). We established the following exclusion criteria for studies to be analyzed: subjects <18 years-old, pregnant women, maternal hemorrhage and breast-feeding. We screened 7264 titles, a total of 195 articles were manually reviewed and 58 were selected as relevant (Fig. 1S). We excluded opinion articles, case series, commentaries; whereas we focused randomized clinical trials, meta-analysis, systematic reviews, clinical

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guideline and scientific society recommendations. Areas of uncertainty were discussed within the panel.

3. Results

3.1. Major advances in pathogenesis of ID

IDA is a microcytic anemia, which defines a decrease mean red cell volume (MCV) as a consequence of reduced hemoglobin (Hb) production. This seems to be related to the absence of negative control of Hb concentration on mitotic processes of late stage erythroblasts [4–6]. ID with or without anemia accounts for approximately 80% of microcytosis; whereas, rare inherited defects of iron metabolism, of globin chains and heme synthesis account globally for almost 20% of microcytic anemias [6,7].

Recent studies suggest that an optimal iron homeostasis is the main driver of normal erythropoiesis. Iron metabolism is highly and finely regulated by multiple crossing pathways, which contribute to the iron recycling after red cell destruction by the reticuloendothelial system as well as the absorption of 1 mg of iron from nutrition sources. This ensures the availability of 25 mg of iron, required for normal red cell daily production [8–10].

Molecular and functional studies have identified different proteins involved in iron metabolism such as the iron membrane transporters (DMT1 and ferroportin) located on enterocytes, the iron reductase enzyme required for Fe bivalent-trivalent modification, the plasma iron transporters and cell storage (transferrin and ferritin) and iron controller (IRP1 and IRP2 HFE, hepcidin) [10,11]. Among the novel identified systems, hepcidin (Hamp) represents a crucial actor in iron metabolism and it is the major controller of iron levels in the body. It is produced by liver cells and acts on ferroportin, causing its internalization and destruction. Iron overload and inflammatory states stimulate Hamp gene expression; whereas, anemia, iron deficiency and stressed erythropoiesis repress Hamp [6].

Plasma iron levels regulate Hamp production by transferrin, which, on binding iron, serves as a ligand for two hepatocellular receptors: transferrin receptor 1 (TfR1) and 2 (TfR2). These crosstalk with a matriptase named transmembrane protease serine 6 (TMPRSS6), which participates to pathways involved in Hamp expression. Mutations in TMPRSS6 gene cause severe microcytic anemias [6,11–13].

3.2. Major advances in diagnosis of IDA

A clinician approaching a subject with mild to severe microcytic anemia should always begin by patient' s history (timing of the appearance of symptoms of anemic syndrome) and by asking whether previous iron supplementation (which type, how long and how many times over the last 2–3 years) has been already prescribed. In their making-decision process, clinicians have to carefully consider fragile and high-risk subset of patients such as elders or individuals with chronic diseases affected by CKD, IBD or HD (Fig. 1).

Microcytic anemia is defined by MCV < 80 fL, hypochromic red cells > 6% or MCH < 25 g/dL and reticulocyte hemoglobin content-CHr < 29 pg (Table 1; Fig. 1) [3,14,15]. International guidelines agree on key blood tests to be carried out for the diagnosis of IDA [3,16]. Up to now serum ferritin and transferrin saturation are the key tests in early decision-making process to identify IDA. Marker of inflammation such as CRP has to be evaluated in order to exclude a possible co-existing chronic inflammation disease. Based on these parameters, we identified (i) an absolute iron deficiency, when the total body iron stores are depleted; and (ii) a functional iron deficiency, when the body iron mobilization is altered and does not meet the iron demand for the erythropoiesis [17]. Soluble transferrin receptor (sTfR) and sTfR-ferritin index (sTfr-F) have been proposed as complementary parameters to identify IDA in presence of possible confounding factors such inflammation that affects serum ferritin levels (Table 1) [5,17–20]. In addition, the determination of Hamp serum levels may be another interesting new tool in diagnosis of iron refractory iron deficiency anemia (IRIDA) or in presence of confounding factors such as inflammation (Table 1). However, their use is still limited due to the lack of studies on large population and of international standardization threshold transferable to clinical routine processes [5,17–22].

3.3. Work-up for diagnosis of IDA in patients in internal medicine setting

Starting from microcytosis, we developed an algorithm for diagnosis of ID/IDA based on serum ferritin levels (SF) and percentage transferrin saturation (TST) combined with rigorous analysis of patient history. As shown in Fig. 1, the initial evaluation step of a patient with hypochromic microcytic anemia is to exclude the possible presence of β-thalassemic-trait, especially for the subjects in/from endemic areas. Using SF and TST values, we identified three subsets of subjects with microcytic anemias:
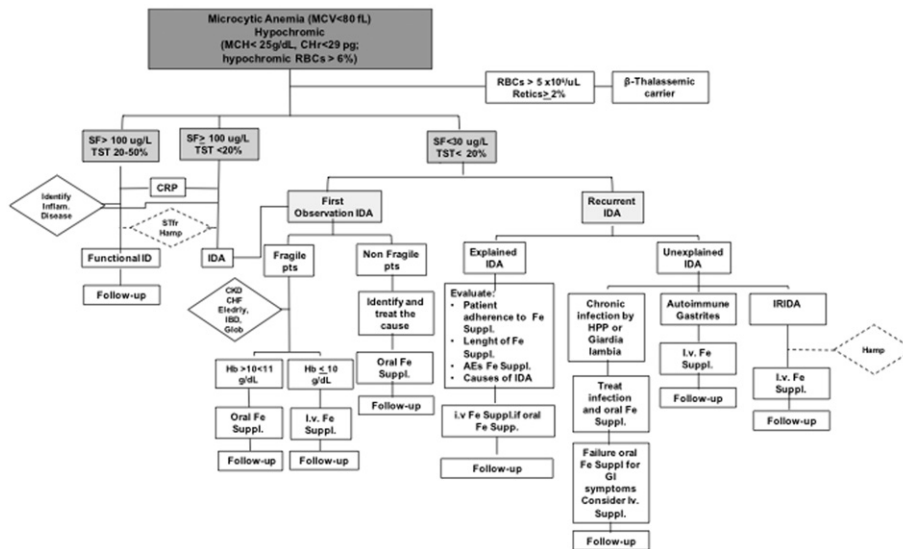

Fig. 1. Proposed algorithm for diagnose and treatment of iron deficiency anemia. MCV: mean cell volume; MCH: mean cell hemoglobin, CHr: reticulocyte hemoglobin content; RBCs: red blood cells; SF: serum ferritin: TST: transferrin saturation; ID: iron deficiency; IDA: iron deficiency anemia; Suppl.: supplementation: Fe: iron; Hb: hemoglobin; sTfr: soluble transferrin receptor; CRP: C reactive protein; Hamp: hepcidin; pts.: patients; CKD: chronic kidney disease; IBD: inflammatory bowel disease; CHF: chronic heart failure; GIob: gastrointestinal occult bleeding; IRIDA: iron refractory iron deficiency anemia; inflamm.: inflammatory.

Table 1
Microcytic anemia: main causes and screening tests.

	Nutritional deficiency	Absorption deficiency	IRIDA	ACD	β-Thalassemic trait
RBCs (cells/uL)	↓	↓	↓	↓→	↑
Hb (g/dL)	↓	↓	↓	↓	↑→
MCV (fL)	↓	↓→	↑→	↓→	↓
Reticulocytes (cells/uL)	↓	↓	↓	↓	↓↓
CHr (g/dL)	↓→	↓	↑→	↓→	↓→
CRP (mg/dL)	→	→	→	↓↓	→
%Transferrin saturation	↓	↓	↓	→	↓→
Ferritin (ng/mL)	↓	↓	variable	↑	→

RBCs: red blood cells; Hb: hemoglobin; MCV: mean cell volume; CHr: reticulocyte hemoglobin content; CRP: C reactive protein; IRIDA: iron refractory iron deficiency anemia; ACD: anemia of chronic disease.

patients with (1) SF > 100 µg/L and TST 20–50%; (2) SF > 100 µg/L and TST < 20%; (3) SF < 30 µg/L and TST < 20% (Fig. 1). To identify the presence of IDA within the first two groups characterized by SF > 100 µg/L, we suggest to measure CRP levels, to define whether there is an underlying active chronic inflammatory disease. TST helps in dissecting functional ID from IDA especially in this subset of patients (Fig. 1). IDA is recognized in patients with either SF ≥ 100 µg/L and TST < 20% (IDA in chronic inflammatory disease) or SF < 30 µg/L and TST < 20%. The following step is to define the timing and the possible recurrence of IDA (Fig. 1). In a new diagnosis of IDA, patient fragility is important to be identified in order to offer the more effective therapeutic approach (Fig. 1). Based on the revision of the literature, fragile patients are defined as subjects with: chronic kidney disease and/or chronic heart failure and/or elderly [3,5,23–29]. In these, we propose hemoglobin (Hb) levels to be used in treatment choice (Fig. 1).

In recurrent IDA, a careful collection of patient history will help in defining whether it is a recurrent explained IDA or an unexplained IDA (Fig. 1). Concerning the recurrent explained IDA, the following causes should be always investigated: (i) original cause of IDA; (ii) patient adherence to the iron supplementation; (iii) length of iron supplementation; (iv) adverse events related to iron supplementation (i.e. GI symptoms) (Fig. 1).

In presence of unexplained recurrent IDA, physician should consider (i) gastrointestinal disorders such as autoimmune gastritis, chronic infection by *Helicobacter pylori* or *Giardia lambia*; or (ii) hereditary disorders of iron metabolism such as iron resistant iron deficient anemia (IRIDA) (Fig. 1).

The detail approaches to special subset of patients is discussed in the following paragraphs.

3.3.1. Chronic renal disease (CKD)

Microcytic anemia might increase the biocomplexity of anemia in patients with end-stage chronic renal disease (CKD) (Fig. 1, Table 2) [30,31]. In fact, the inadequate production of erythropoietin might be further aggravated by ID, which contributes to hypo-responsiveness to erythropoiesis of stimulating agents (EASs). The occurrence of ID in CKD with the appearance of microcytic anemia is mainly related to different synergizing factors: (i) reduced intestinal iron absorption and (ii) chronic inflammatory state [32–35]. The diagnosis of IDA in CKD is based on serum ferritin levels and transferrin saturation percentage (Table 2). In addition, the percentage of hypochromic red cells (>6%) and reticulocyte hemoglobin content-CHr (<29 pg) might be useful tools in treatment and follow-up of CKD patients with IDA [34,36].

3.3.2. Chronic heart failure (CHF)

Growing evidences indicate that ID is an important novel comorbidity of chronic heart failure (CHF) with or without microcytic anemia (Fig. 1, Table 2). Since subjects with CHF might be considered as fragile patients, they require special attention. In CHF, two main factors sustain ID: patients aging and chronic inflammation state due to failing heart function, which affects Hamp system and increases ferritin levels [28,

37–42]. Different studies have shown that the prevalence of ID increases with heart failure severity, most likely related to the cumulative effects of different mechanisms: (i) worsening chronic inflammatory state; (ii) anorexia; (iii) GI mucosal oedema and decreased gastric and intestinal motility; (iv) decreased mesenteric blood flow and (v) frequent blood tests [42–44]. The recent observation of increased rate of hospital re-admission for CHF patients compared to individuals with CHF without ID, strongly support the impact of ID/and or IDA on CHF [28,29,45–47]. Thus, in CHF patients, the identification and correction of ID/IDA should be considered as part of comprehensive clinical management of CHF.

3.3.3. Elderly patients

In elderly, normocytic or microcytic anemia deeply influences patient mortality and quality of life by (i) decreasing physical performance and cognitive function; and (ii) increasing number of falls and hospitalization (Fig. 1) [22,24,48]. IDA and anemia of chronic diseases (or functional ID) are the main causes of anemia in older adult. Although different factors contribute to ID in elderly patients, malnutrition, delay gastric emptying and occult blood loss are the main causes of ID in aged subjects [22,49]. In addition, the decline of biological and cognitive functions associated with reduced appetite and diminish senses of taste further contribute to inadequate dietary intake and absorption [22,49]. In this context, the definition of anemia based on Hb levels in elderly requires a cut-off different from that defined by WHO for adults [48,50]. Up to now, Hb levels lower than 12 g/dL are commonly considered indicative of anemia in older adults in both sexes [48,50]. The interpretation of markers of iron status in elderly is complicated by the presence of concomitant chronic disorders, which might affect serum ferritin levels and the profile of anemia. Thus, an appropriate cut-off value for serum ferritin might be proposed in screening anemia in elderly (Fig. 1 and Table 2). This is in combination with percentage of TS and CRP allows the identification of IDA and functional ID [48,50].

3.3.4. Gastrointestinal (GI) disorders

In adulthood, different gastrointestinal disorders might be associated with microcytic anemia due to ID. In men and post-menopausal women, occult gastrointestinal bleeding accounts for the large part of IDA (Table 2). In older subjects (1–10% of patients as reported by Goddard et al.) [51], dual pathologies involving upper and lower GI system should always be considered during the diagnostic process for IDA. Malabsorbtion related diseases account for a subset of patients, who might develop IDA (Table 2). Among them, gastrectomized individuals require special attention when microcytic anemia is detected, due to the increase risk of gastric cancer development [51].

Recent studies have linked chronic infection by *Helicobacter pylori* (HP) to the development of recurrent IDA (Fig. 1, Table 2) [6,15,52]. The eradication treatment for HP beneficially impacts iron homeostasis, as supported by the amelioration of ferritin levels. In addition, the proton pump inhibitors seem not to contribute to the iron deficiency [51].

Inflammatory bowel diseases (IBD) are also characterized by IDA, which impacts patient QoL (Table 2). Although clinicians are awarded

Table 2
Diagnosis and therapeutic options in special subset of patients affected by microcytic anemia related to ID.

Disease	Causes of ID	Diagnosis	Clinical management	Follow-up	Notes	Ref.
GI disorders	Occult blood loss • NSAID use • Colon carcinoma • Benign gastric ulcer • Gastric cancer	Microcytic anemia SF <30 ng/mL TST < 20%	• Remove the cause • Oral Fe suppl.	Hb levels after 4 weeks and then every 3 months the iron related indices for the first year then once/y	- Verify tolerability and patient adherence to oral Fe suppl. - Consider iv Fe suppl. if failure after 6 months suppl.	
	Malabsorpition • Coelic disease • Gastrectomy • Infection (HP, Giardia l.) • Quiescent D.	Microcytic anemia SF <30 μg/L TST < 20%	• i.v. Fe suppl is indicated. i.v. Fe suppl. is preferred	Hb levels after 4 weeks and then every 3 months the iron related indices for the first year then once/y	Microcytic anemia is still undertreated in IBD patients	[3,6,15,23,24,25,26,27,28,29]
	IBD (Disease activity) • Active D.	Microcytic anemia SF <100 ng/mL TST < 20%	Treat the active IBD Absolute indication for i.v. Fe suppl are: • Hb < 10 g/dL • Intolerance to oral Fe suppl. • Inadequate response to oral Fe suppl. • Severe intestine D. erythropoiesis			
CKD Functional ID: Normocytic anemia SF:100–800 ng/mL TST: >20%	• Reduced Fe absorption related to chronic inflammatory state • Relative EPO deficiency • Uremic induced inhibition of			Not yet on HD: Microcytic anemia SF < 100 ng/mL TST < 20% On HD: Microcytic anemia SF < 200 ng/mL	Oral Fe suppl.: 30% of pts. shows GI side effects: consider i.v. Fe suppl. i.v. Fe suppl.: well tolerated.	• Hb levels after 4 weeks with 1–2 g/month increase • Evaluation of pts QoL improvement • ↓ %hypochromic RBCs
Chronic heart failure (CHF)	• Reduced Fe absorption related to chronic inflammatory state • Nutritional factors • Suboptimal mesenteric blood flow	SF[a] <100 ng/mL SF:100–300 ng/mL and TST < 20%	i.v. Fe suppl has to be considered due to: • low pts. adherence to oral therapy • suboptimal mesenteric blood flow (↓ absorption and politherapy)	[3,30,31,32,33,34,35,36] Hb levels after 4 weeks and then every 3 months the iron related indices for the first year then once/y In anemic pts consider Hb target >7 g/dL	ESAs should be considered only in presence of chronic renal failure	[3,37,38,39,40,41,42,43,44,45,46,64]

Table 2 (*continued*)

Disease	Causes of ID	Diagnosis	Clinical management	Follow-up	Notes	Ref.
	• Malnutrition • Delay gastric emptying • occult blood loss	Microcytic anemia SF < 30 ng/mL TST < 20%	• Identify and remove the cause; • Oral Fe suppl. fractioned in small doses.	Hb levels after 4 weeks and then every 3 months the iron related indices for the first year then once/y Hb target >8 g/dL	- Functional ID as normocytic anemia: • SF: >100 ng/mL • TST: >20% • ↑ CRP	[3,22,47,48,49,50]
Elderly	• Presence of chronic inflammatory diseases	Anemia SF < 30–100 ng/mL,TST < 20% ↑ CRP	i.v. Fe suppl. has to be considered if: • GI intolerance to oral Fe formulation • GI disorders • Presence of co-morbidities: CKD, HD, IBD RBC transfusion should be considered if Hb levels • <6 g/dL (acute setting) • 7–8 g/dL (chronic setting)		- Unexplained normochromic normocytic hypoproliferative anemia, possibly related to stem cell disorder(s) and characterized by: • ↓ CRP	
IRIDA	Autosomal recessive condition	Mutations in TMPRSS6 gene	Microcytic anemia SF ≥ 30 ng/mL TST < 20%	Oral Fe suppl.: high possibility of failure Consider i.v. Fe suppl.	Hb levels after 4 weeks and then every 3 months the iron related indices for the first year then once/y	Hamp →↑	[5,6,9,12,13,15]

NSAID: non steroid anti-inflammatory drug; IBD: inflammatory bowel disease; CHF: chronic heart failure; IRIDA: iron refractory iron deficiency anemia; SF: serum ferritin; TST: transferrin saturation; ESAs: erythropoietic stimulating agents; pts.: patients; QoL: quality of life; RBCs: red blood cells; Hamp: hepcidin; suppl: supplementation.

a   The cut-off for SF without transferrin saturation has been selected by Task force for diagnosis and treatment of acute and chronic heart failure of the European society of cardiology and by the American college of physician.

of IDA in IBD, microcytic anemia is still under treated in these patients [23,51,53–56]. IDA in presence of active IBD requires the combined therapeutic approach of primary disease treatment and ID correction.

3.3.5. Iron restricted iron deficiency anemia (IRIDA)

IRIDA is the most common inherited condition of iron metabolism characterized by microcytic anemia (Tables 1, 2). IRIDA is caused by mutations in *TMPRSS6* gene. Usually MCV is lower than in the other conditions of IDA and transferrin saturation is always very low with low/normal serum ferritin (Tables 1, 2). Hamp levels are either normal or increased compared to healthy subjects. RCP is negative and this allows the physician to differentiate it from ACD. IRIDA generally should be suspected in presence of recurrent IDA with unexplained causes, characterized by several failures of oral iron supplementation (Fig. 1) [9, 12,13].

3.4. Major advances in treatments of IDA

Being ID the main cause of microcytic anemia in patients admitted to Internal Units, the treatment is based on iron supplementation, as oral iron or intravenous iron administration (Table 3). The choice on iron supplementation is based on Hb levels, the tolerance to oral iron supplementation and the presence of concomitant disease, which might affect iron absorption (Table 3). The failure of oral iron supplementation might be related to either low patient adherence to the therapy (i.e.: treatment discontinuation, low tolerance mainly due to GI symptoms) or to true refractoriness (Fig. 1 and Table 3) [5,6,14,23,25,57–62]. Since Hamp plays a key role in iron absorption and homeostasis, different studies have evaluated Hamp response to acute oral iron supplementation. Morretti et al. have recently showed that 48 h are required to clear the effect of Hamp release in response to acute oral iron administration [57]. This study supports the introduction of alternative day schedule in place of daily administration of oral iron to overcome the Hamp mediated block of iron absorption. This might ameliorate iron absorption and improves patient tolerability to oral iron supplementation (Table 3). Oral iron supplementation should be maintained for 3 to 6 months to replete the iron stores and normalize ferritin level.

Intravenous iron administration is definitively more effective in correction of ID since it by-passes the iron absorption step. Although its costs are higher than oral iron supplementation, it offers several advantages such as (i) rapid repletion of iron stores; (ii) single dose sufficient for most of the new i.v. formulation with a reduction in hospital visits (Table 3) [6,63]. This latter is limited to the more recently developed molecules, which are characterized by a core that contains the iron salt surrounded by a shell, allowing the reticuloendothelial system to process and release iron for erythropoiesis and storage (Table 3) [5,6, 14,23,25,57–62]. Although adverse events have been reported for i.v. formulation, the cost-benefit ratio is in favor of i.v. supplementation as also indicated by the European Medicines Agency (EMEA: http://www.emea.europe.eudocument WC500150771, 2013), introducing

Table 3
Major iron formulations available and current treatments for ID.

Treatment	Agent	Dosage	Amount of Fe administrated (mg)	Adverse events	Recommendations	Ref.
Oral iron suppl.	Ferrous Ssulphate	1 tablet/day	(Fe^{2+}) 85–105 mg	• Nausea • Vomit • Epigastric disconfort • Constipation/diarrhoea • Metallic taste • Dark colored stools	• Healthy population after treatment of underlying cause of IDA; • Elderly if Hb > 8 g/dL < 12 g/dL;	[3,5,6,14,26,51,52,53,54,56,60]
	Ferrous gluconate	1 tablet/day	(Fe^{2+}) 75–80 mg			
	Na^+ ferrigluconate	1 fl/day	(Fe^{3+}) 62.5 mg		Gray area: Every day or alternative day schedule.	
	Fe-glycine sulphate	1 tablet/day	(Fe^{2+}) 100 mg			
	Fe-bisglycinate	1–3 tablet/day	(Fe^{2+}) 25 mg			
	Lyposomial Fe-pyroph and Vit. C	1–2 tablet/day	(Fe^{2+}) 30 mg and Vit. C 70 mg			
I.v. Iron suppl.	Na^+ ferrigluconate	1–2 fl/day- diluted in FS	(Fe^{3+}) 62.5 mg	• Nausea • Vomit • Pruritus • Headache and flushing • Myalgia and arthralgia • Back and chest pain (resolution within 48 h) Notes • Avoid iv Fe suppl. during the first trimester of pregnancy (no data available on safety) • Test-dose is NOT informative on possible severe AEs.	Strong indication in: • CKD stage 5D • IBD with active disease • Malabsorption • CHF • Hb ≤8 g/dL • IRIDA • IDA with intolerance to oral Fe suppl. Suggested in: • CKD stage 3D-5D	[3,5,6,13,14,26,31,36,51,52,53,54,55,56,57,58,59,61,62,63,64]
	Ferric carboximaltoside	500–1000 mg diluted in SS	(Fe^{3+}) 100–500 mg			
	Fe-saccharate	1 fl/day diluted in SS	(Fe^{3+}) 100 mg			
	Ferumoxytol	510 mg	(Fe^{3+}) 510 mg		Gray area: IDA in elderly	

Vit.C: Vitamine C; fl: SS: saline solution; i.v.: intravenous; CKD: chronic kidney disease; CHF: chronic heart failure; IBD: inflammatory bowel disease; Hb: hemoglobin; IDA: iron deficiency anemia; Hamp: hepcidin; IRIDA: iron refractory iron deficiency anemia; hrs: hours; D: disease; suppl: supplementation.

Ganzoni formula calculates the amounts of iron required to restore desire Hb levels: iron deficit (mg) = body weight (Kg) × (target Hb-actual Hb) (g/dL) × 2.4 + iron storage depot (mg).

strategies to minimize adverse events [64]. A large revision of the literature on the safety of different iron i.v. formulations has concluded that i.v. iron therapy is not associated with increased risk of severe adverse events (AEs), even in patients with history of heart failure or of infections [62].

The follow-up schedule of iron-supplementation therapy is based on the evaluation of Hb levels at 4 weeks of treatment. Recently, the day-14 Hb levels have been proposed in decision-making process to move patient from oral to i.v. administration in case of failure [14].

In special subset of patients such as elderly, CKD, IBD and CHF subjects, rapid correction of IDA is important and generally required an intensive therapeutic approach with maximized tolerability (Table 3).

IBD patients with quiescent disease generally feel uncomfortable with oral iron supplementation mainly due GI AEs [54,65]. Thus, i.v. route should be preferred in IBD patients, according to the available guidelines (Table 3) [23,51,53–56].

In CKD, iron oral supplementation is recommended in patients with IDA not receiving ESAs and not on HD [66]. Whereas, i.v. iron should be proposed to subjects under ESAs treatment and/or on HD, based on the evidence that oral iron does not sufficiently support ESAs stimulated erythropoiesis [31,36,67,68]. Up to now it is still not clear whether the high dose low frequency or low dose high frequency strategy might be the best option in these patients [31,36,67,68]. In addition, frequent re-evaluation of SF and TST combined with Hb levels should always be carried out to avoid iron-overload, which has been recently reported in CKD subjects longtime treated with i.v. iron supplementation [31].

In subjects with CHF, iron supplementation and correction of anemia improve (i) New York Heart Association (NYHA) functional classes; (ii) exercise capacity and (iii) patients QoL [42–44,69]. Thus, iron supplementation should be always considered as part of clinical management of CHF patients.

In elderly, IDA affects QL, cognitive function and worsened chronic organ diseases, deeply affecting patient mortality and morbidity [3,34,59,70]. Thus, iron supplementation has to be introduced in these patients. However, it should be always considered the final objective of this treatment and the cost/benefit ratio of iron supplementation in elderly.

In IRIDA patients, oral iron administration usually does not solve the problem, whereas i.v. iron temporaly ameliorate this condition. Ferritin levels could be reduced or normal after iron treatment [6,13].

3.5. Areas of uncertainty

In adult patients admitted to Internal Medicine setting, the diagnosis and the management of IDA should receive great attention and be considered as target of intervention. However, various aspects of IDA treatment and route of administration in different subset of patients are still uncertain. In elderly, large clinical trials to better identify the final objectives of the iron supplementation and the route of administration (oral or i.v.) are needed. The lack of general recommendation in these fragile patients might result in under-treatment of IDA. In CHF subjects, the recent guidelines propose the use of i.v. iron supplementation in patients

with ID even in the absence of microcytic anemia [59]. This recommendation is based on clinical trials [42–44], although no data are available on the timing and duration of iron supplementation.

In patients with anemia related to chronic diseases (ACD), it is crucial the identification of absolute ID, since ID is often functional. In ACD, the clinical management of absolute ID is still largely a physician choice, which is based on patient clinical status, clinical stage of the disease especially for cancers as well as the cost/benefits ratio [71].

Since one the main are of uncertainty is the treatment of fragile patient further work is required to better define the route of administration of iron supplementation and the therapeutic endpoints of iron supplementation.

4. Discussion

Functional or absolute iron deficiency associated with microcytic anemia is common in adult patients in Internal medicine setting. This is especially true for fragile patients such as subjects with IBD, CKD, CHF and in elderly. Global burden studies reveled that ID is one of the top cause-specific anemia burden, representing a target of intervention for both physician and national-international health programs.

Although progresses in pathogenesis and diagnosis of IDA have ameliorated in the last decades, the decision-making processes facing IDA still requires a comprehensive patient evaluation and cost/benefit estimation.

This review has some limitations since we excluded children and fertile women with IDA due to gynecologic or obstetric causes (i.e. maternal hemorrhage and/or menometrorrhagia), who represent a large portion of IDA in adulthood [1].

Finally, in Internal Medicine Units, a large part of patients is represented by fragile subset. They require a rapid identification of the causes underlying IDA and a specific treatment to improve their outcomes.

Concerning the out-patients with recurrent unexplained IDA, more rare condition of IDA related to inherited disorder or GI infections or autoimmune gastrite should always be considered and excluded.

The improvement of iron preparations for i.v. supplementation, have impacted: (i) the safety; (ii) the patient satisfaction; (iii) the health costs by reducing the number of hospital visits; and the in-stay hospital (iv) the welfare spending by the reduction of patient disability and the level of sickness absence from jobs. Thus, special program of intervention should be designed and set-up at national and international level to early identify and treat microcytic anemia related to ID.

5. Conclusions

In internal medicine setting adult patients are characterized by multimorbidity and poli-pharmacologic treatments, which might affect the erythropoietic compartment, contributing to anemia and iron deficiency. The early identification the underlying causes of IDA may lead to a target therapeutic approach, combined with iron supplementation. Fragile patients such as subjects with IBD, CKD, CHF and elderly represent a growing population requiring early and special care attention. Multicentric trials in subsets of adult fragile patients are needed to get important information useful in clinical practice. Although recommendation and guidelines are important in decision-making process, these authors strongly suggest that a reasoned and personalized medical treatment focused on each patient clinical profile is the most powerful approach to iron deficiency anemias.

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Learning points

• Global burden disease studies show that iron deficient anemia (IDA) is one the main cause of increased years-life lived-with-disability (YLD) in all ages and both sex.

• IDA affects a large part of adult and elderly patients admitted to Internal Medicine Units.
• The available evidences indicate that (i) recurrent IDA should always be investigated, considering uncommon causes; (ii) IDA might worse the performance and the clinical outcome of fragile and high-risk patients and might require an intensive treatment.

Authors contributions

LDF and MDC have full access to all data and take the responsibility for data integrity and analysis. Study concept and design: MDC, AI LDF; Acquisition, analysis and interpretation: LDF, MDC, AT, AI. Critical revision of the manuscript: AI and AT. Drafting of the manuscript: MDC, AI, LDF.

Authors disclosures

LDF, AI, MDC and AT have nothing to disclose.

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