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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.

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:

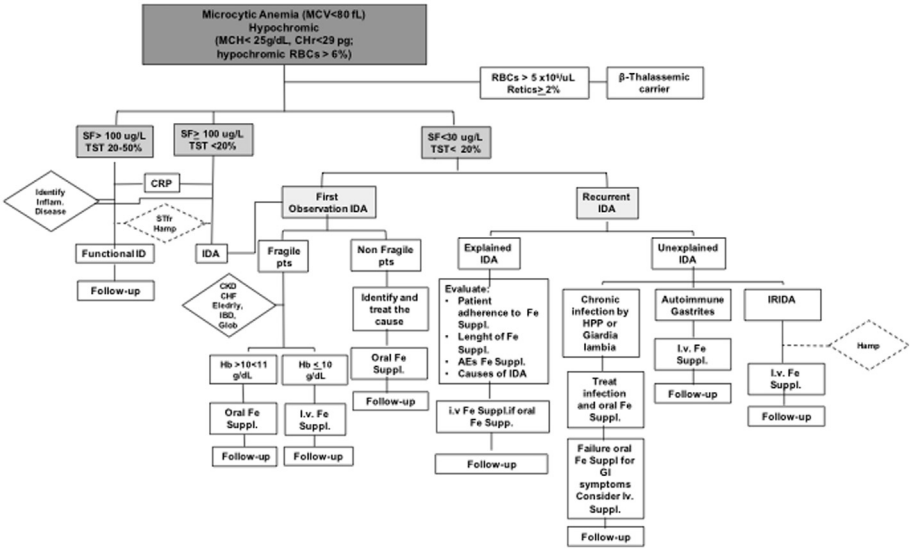

Fig. 1. Proposed algorithm for diagnose and treatment of iron deficiency anemia. MCV: mean cell volume; MCH: mean cell hemoglobin, CHr: reticulocyte hemoglobin content; RBCs: red blood cells; SF: serum ferritin: TST: transferrin saturation; ID: iron deficiency; IDA: iron deficiency anemia; Suppl.: supplementation: 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.

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