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ANEMIA IN THE ELDERLY

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Abstract:

Introduction: *Anemia is an important risk factor in the development of several complications and morbidities especially in the elderly. It is associated with higher rates of hospital admissions worse survival outcomes. Anemia in the elderly is divided into 4 main types according to cause: nutrient deficiencies anemia, chronic disease (chronic inflammation), chronic kidney disease, and unexplained anemia. The risk of anemia increases after an individual passes fifty years of age, with a prevalence of more than twenty percent in individuals older than eighty-five years, therefore, it is important to establish the best ways to approach anemic seniors and determine best work-up methods.*

Aim of work: *In this review, we will classify the common types of anemia in the elderly population and discuss the most recent approaches for management of anemia in the elderly.*

Methodology: *We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1985, through February 2017. The following search terms were used:*

Anemia, elderly, management, anemia of chronic diseases, unexplained anemia, elderly anemia evaluation, recent advances

Conclusions: *The main challenge in the management of anemia is the proper assessment and evaluation of the condition as this will determine later treatments and management plans, thus knowing the cause is essential to determine. Most common causes of anemia in the elderly population include the presence of a chronic disease, the presence of a nutritional deficiency (most likely iron), or chronic kidney disease. Chronic blood loss is also an important cause that will eventually lead to the development of an iron deficiency anemia. Chronic blood loss could be an indicator of serious illnesses like colorectal cancer, therefore, it should be taken seriously. Treatment of anemia usually aims at achieving two outcomes: target the underlying cause and treat it (if possible) and improve blood quality. If underlying cause cannot be treated, or acute blood loss is present, blood transfusion can be indicated to give a rapid recovery of blood stores. Later, the use of recombinant erythropoietin will improve the general condition.*

Key words: *Anemia, elderly, management, recent advances*

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INTRODUCTION:

The deficiency in red blood cells, reduced hematocrit and hemoglobin, is the definition of anemia. Hemoglobin (HB) is the metalloprotein (contains iron) that transport the oxygen inside the red blood cells throughout the body [1].

The insufficiency of oxygen is lethal for the cells and can cause organs' malfunction and, if it continues, even organ disability [2]. Thus, Anemia is a pathologic condition that has to be compensated. While anemic younger patients may depend on their organ reserves to compensate the insufficiency of oxygen, older patients >65 years with anemia are disadvantaged on this point, because aging is cause a progressive loss of functional organ reserves, making the risk of frailty high [3]. Anemia is a common problem in elderly and is related with increased physical weakness, frailty, cognitive decline, depression, and mortality [4-7].

The cohort study of the Third National Health and Nutrition Examination Survey (NHANES III) has shown that the prevalence of anemia in patients older than 65 years is as: in men (hemoglobin, Hb <13 g/dL) the prevalence is 11% and in women (Hb < 12g/dL) it is 10%.

About 30 % of anemic patients had a nutrient deficiency (mostly iron deficiency), whereas the other 60% were divided between "anemia of chronic inflammation" and "unexplained anemia" [8]. A newer study examined anemia prevalence and incidence in a longitudinal manner and showed that whereas the prevalence of anemia is 5% to 7% at 65 years, it increases rapidly with age, exceeding 40% in people who are older than 80 years. Again, anemia is consistently mild, with the prevalence of severe anemia (Hb<8 g/dL) shown to be less than 0.5% [9].

Anemia is usually mild and asymptomatic; however, it is related with high rate of morbidity and mortality as assessed in large cohort studies. Anemia is an independent predictor of these adverse outcomes both in healthy community-dwelling subjects and in patients with significant co-morbidities.

It has been focused on the inflammatory process, the resistance against erythropoietin, the response of the hematopoietic stem cells to the decrease in red cell mass related to aging; to detect the pathophysiology of the "unexplained" anima particularly, and all cause anemia in general.

METHODOLOGY:

• Data Sources and Search terms

We conducted this review using a comprehensive search of MEDLINE, PubMed, and EMBASE, January 1985, through February 2017. The following search terms were used: Anemia, elderly, management, anemia of chronic diseases, unexplained anemia, elderly anemia evaluation, recent advances

• Data Extraction

Two reviewers have independently reviewed the studies, abstracted data, and disagreements were resolved by consensus. Studies were evaluated for quality and a review protocol was followed throughout.

The study was approved by the ethical board of King Abdulaziz University Hospital

Anemia Classification

It is difficult define the main cause of anemia in the elderly because of the specialty of having multiple health problems and polypharmacy. In the NHANES III, for example, nearly, 60% of subjects with anemia had 2 or more age-related diseases. Though, anemia in the elderly is generally divided into 4 main types according to cause: nutrient deficiencies anemia, chronic disease (chronic inflammation), chronic kidney disease, and unexplained anemia [8].

Nutrient deficiency anemia

About 30% of anemia in old people back to iron, folate, and/or vitamin B_{12} deficiencies [8]. Iron deficiency alone is about 50% of the nutrient deficiency-related anemia cases. The main cause of iron deficiency anemia in the elderly is the blood loss through gastrointestinal lesions, whereas some other cases results from regimen [10].

When 100 iron deficiency anemic patient had gastrointestinal endoscopy, 62% of them had a lesion that could cause blood loss and 16% had premalignant polyps or colon malignant tumor [11]. Serum ferritin concentration is measured when diagnosing anemia, it gives us an idea about the iron storage, however, it increases in the older patient due to age-related disease, which makes diagnosing anemia in old patient difficult. A study of older patients (80 years and older) showed that it is difficult for to detect iron deficient patients by the routine blood tests of serum iron, transferrin saturation, and ferritin, because it had poor screening sensitivity [12]. The more sensitive test that has become widely used is transferrin receptor-ferritin ratio, Although prevalence of iron deficiency anemia in the elderly based on the routine blood tests may be

underestimated in NHANES III [8], a recent representative study of older adults used the transferrin receptor-ferritin ratio showed that 16.7% of anemia cases were related to iron deficiency anemia (similar to the 16.6% estimate from NHANES III) [13].

The deficiencies of vitamin B_9 and vitamin B_{12} are also common cause of anemia in the elderly and forms about 14% of all anemia cases. The classification of vitamin B_{12}deficiency in the NHANES III is not sufficient because it cannot detect all the subclinical cases of vitamin B_{12} deficiency, because it was based on serum concentration [8]. If methylmalonic acid testing had been used in NHANES III, then the prevalence of vitamin B_{12} deficiency anemia would be a bit higher than the assessments, because the information from methylmalonic acid test with the information from homocysteine concentration would have helped to detect more cases of mild vitamin B_{12} deficiency [14].

Anemia of chronic disease

Infection or chronic disease can also cause anemia due to chronic immune activation and inflammation. About (19.7%) of anemia in older adults is associated with chronic inflammation and is called anemia of chronic disease [8]. However, it is very hard to differentiate anemia of chronic inflammation from iron deficiency anemia in older adults because of the complications of gastrointestinal bleeding as well as the effects of medications. It is probable that in the NHANES III the prevalence of anemia of chronic inflammation is overestimated in the expense of anemia from iron deficiency because when the two types of anemia are both present, serum ferritin levels may be normal. Indeed, even differentiating anemia of chronic inflammation from anemia of chronic kidney disease is somewhat not important given the emerging evidence that there is increased inflammation associated with renal function in older adults without chronic kidney disease. Because of the multiple clinical and subclinical morbidities in the elderly, as well as the high levels of proinflammatory cytokines that come with aging, determining the underlying factor of anemia of chronic inflammation in the elderly is very hard [15].

Chronic kidney disease related anemia

Chronic kidney disease leads to anemia because it may damage the production of erythropoietin. In NHANES III, 8% of anemic older subjects had renal dysfunction with creatinine clearance lower than 30 mL/min and another 4% of anemia cases had both renal dysfunction and anemia of chronic inflammation [8]. However, just a few studies have distinguished the association between renal function and anemia in the elderly. In general, these researches show that there is a threshold of renal function, the risk of anemia raises below it, but this threshold value changes between studies, ranging from 30mL/min to 60mL/min [16].

Unexplained anemia

About 30% of the anemic elderly in the NHANES III could not be classified as nutrient deficiency, chronic inflammation, or chronic kidney disease anemia because they did not meet the criteria for that, and were classified as "unexplained anemia" [8]. significantly, other groups have also showed that nearly 30% of anemia cases were unexplained in different samples of the elderly [17]. However, it is probably that some of unexplained anemia cases are related to myelodysplastic syndrome (MDS), a hematologic problem that is common in the elderly. Guralnik et al. liberally estimated that more than 17.2% of unexplained anemia cases (5.8% of all anemia cases) might be caused by MDS by examining the co-occurrence of neutropenia, thrombocytopenia, or macrocytosis with unexplained anemia. Though, an essential proportion of anemia cases (nearly 25%) would stay unexplained even after considering for MDS [8].

Evaluation of anemia

The mean corpuscular volume (MCV) has been used in order to evaluate an anemic patient, followed by biochemical tests [18]. The MCV has been shown to add value to the RDW (red cell distribution width) for evaluation of macrocytosis [19]. However, for microcytic anemias, especially for iron deficiency anemic patients, MCV is of less value. About 22% of older adults may be diagnosed with iron deficiency anemia by their response to a course of ORAL iron therapy, although they do not have the standard laboratory findings of ferritin < 30 ng/mL and transferrin saturation < 16% [20]. Anemia of inflammation is usually diagnosed when the ferritin level is high (>200ng/ml), transferrin saturation is low (<16%) [21]. However, although the delivery of iron to red cell precursors is limited because of the low transferrin saturation, seventy percent of patients with anemia of inflammation, have normal MCV. This interfere of these two common etiologies of anemia (iron deficiency and inflammation) has made the use of the traditional markers: MCV, transferrin

saturation, and ferritin, difficult to explain in routine practice [22].

The ways that iron-restricted erythropoiesis may cause anemia are: the absolute iron deficiency; hepcidin-mediated iron reservation [23], and/or a functional iron deficiency due to erythropoietin-stimulated erythropoiesis [24]. Unexpected diseases like chronic kidney disease (CKD) or clinically-silent malignancy, must be considered when anemia is evaluated. If absolute iron deficiency is diagnosed, in the older post-menopausal women it is important to exclude gastrointestinal lesions, specially malignancy as a source of chronic loss of the blood. However, the examination of the gastrointestinal tract is negative in about 30-60 % of such patients. To rule out chronic kidney disease, serum creatinine and GFR must be tested, a nephrology consult will be suitable. For consideration that the anemia is secondary to end stage renal disease (ESRD), the proposed cut-off of glomerular filtration rate (GFR) < 60 mL/min, follows CMS guidelines on reimbursement for erythropoietic stimulating agent (ESA) therapy in patients with ESRD; but between 30–60 mL/min GFR, other causes for anemia may be possible [25].

If transferrin saturation and serum ferritin values are indecisive, more evaluation is needful to exclude absolute iron deficiency or inflammation/chronic disease. As mentioned previously, the improvement after a trial of oral iron ensures absolute iron deficiency. But, insignificant improvement or no improvement at all, after oral iron therapy, might require a trial of intravenous iron, because when hepcidin is present, intestinal iron absorption is damaged. In a study of iron deficiency anemic patients whom clinically diagnosed depending on ferritin and transferrin saturation values, the patients responded to 28 days of oral iron therapy was only 21% , when the percentage of patients responded to intravenous iron therapy was 65% [26].

The diagnosis of the anemia of inflammation or unexplained anemia of the elderly (UAE) is suggested when the improvement to iron therapy is absent. In this case, clinical evaluation for inflammation and laboratory tests for sedimentation rate (ESR), C-reactive protein, erythrocytes, fibrinogen, hepcidin levels, and IL6 can be beneficial [23]. If abnormal, treating the cause completed with an erythropoiesis stimulating agent (ESA) can be useful for further management. Alcohol can be the reason of the poor reserve of the bone marrow or folate deficiency in the elderly so a careful history for alcohol abuse is important specially in patients with an MCV>100. A study by Cash and Sears of 90 patients (mean age 50.9 ± 16.5, not confined to elderly) with anemia of chronic disease (ACD) noticed that there was a wider spectrum of associated diseases with ACD than had previously been noticed [27]. A newer study by Waalen et al. compared a large cohort of UAE cases in the elderly with a matched, non-anemic control group and found that IL-6 and hepcidin levels did not differ significantly; but, testosterone levels were lower in men and erythropoietin levels were inappropriately low for the degree of anemia [28].

Management of Anemia

The management depends on the underlying cause of anemia. Although folate deficiency became less common after adding folate to flour, special attention needs to be paid in particular conditions: e.g. alcoholism combined with poor diet, or compliance failure with folate supplementation in a dialysis patient. As the same, Vitamin B_{12} deficiency may be less common, but a diagnostic trial of Vitamin B_{12} therapy may be needful if the symptoms and signs are consistent with Vitamin B_{12} deficiency. Extra analysis for, homocysteine and methylmalonic acid can be beneficial but may also be indecisive [29].

To exclude absolute iron deficiency, a diagnostic or therapeutic trial involving intravenous iron therapy can be needful. Even the “gold standard” diagnostic bone marrow aspirate indicating the presence of some stainable iron may obscure a deficiency of storage iron, since in some of these cases the patients’ anemia has been shown to be responsive to iron therapy [30].

Thirdly, therapy with an erythropoiesis stimulating agent (ESA) may be indicated for treatment of one of several causes of anemia in the elderly. ESA’s can be useful in treating the anemia in patients with end stage kidney disease; anemia in patients with inflammation/chronic disease who are scheduled for elective surgery; and in patients with MDS who have moderate to severe anemia, in which the only other alternative may be chronic blood transfusions [31].

ESAs were first demonstrated and approved for use to increase the hemoglobin levels in patients with end-stage chronic kidney disease (CKD) undergoing dialysis and subsequently in such subjects who did not require dialysis [32]. Based on prospective randomized trials that demonstrated reduced allogeneic blood transfusion, ESAs have subsequently been approved in patients undergoing elective surgery and in oncology patients with

chemotherapy-induced anemia [33].

Subsequent to FDA approval, clinical trials were undertaken in an attempt to demonstrate long term improved patient outcomes with ESA therapy. Several clinical trials in patients undergoing elective spine surgery, patients with chronic kidney disease (predialysis), and in patients with stage II-IV (New York Heart Association) congestive heart failure. These studies were designed to evaluate aggressive anemia management (to a target Hgb within normal range) vs. conservative Hgb correction. In patients scheduled for elective spine surgery, outcomes were compared for ESA and placebo-treated cohorts who did not receive anticoagulation prophylaxis. In this study a higher incidence of deep vein thrombosis was found in patients receiving epoetin alfa compared to placebo. According to the subsequently revised prescribing information for ESA therapy, antithrombotic prophylaxis should be considered when ESA's are used in elective surgical patients who do not receive perioperative anticoagulation. In anemic patients with congestive heart failure (CHF) a large, randomized trial of patients whose median age was 72.0 (range 63–78), long-term ESA therapy was successful in correcting anemia and reducing blood transfusions, but did not improve long-term clinical outcomes (composite outcome of death or any cause of hospitalization from worsening CHF) [34]. The American Society of Hematology/American Society of Clinical Oncology Clinical Practice guideline update has recommended use of ESAs in patients with low risk MDS, in order to avoid blood transfusions [35]. In clinical practice, the potential for increased risks of death and thromboembolic events should be balanced against the benefits of treatment with ESAs, including avoidance of allogeneic blood transfusions.

Iron supplementation is recommended in patients with ferritin concentrations of <30 ng/mL and TSAT values of <15% (absolute iron deficiency). For iron deficiency anemia, the usual replacement dose is ferrous sulfate, 325 mg (65 mg of elemental iron) per day, or ferrous gluconate, 325 mg (38 mg of elemental iron) per day. However, oral iron is poorly absorbed and is commonly associated with gastrointestinal adverse effects and poor rates of patient adherence. Low-dose iron therapy, with 15 mg of elemental iron per day as liquid ferrous gluconate, effectively corrects hemoglobin and ferritin concentrations with fewer gastrointestinal adverse effects than higher iron doses. Treatment is usually continued for six months to replete iron stores. For persons who fail to respond to oral iron therapy, parenteral treatment with iron dextran or iron sucrose is usually therapeutic [36].

Oral versus intravenous iron therapy

In patients with anemia of inflammation and functional iron deficiency, the use of IV iron supplementation is recommended due to its superior efficacy compared to oral iron. For patients without functional or absolute iron deficiency before the initiation of ESAs, the possibility that functional iron deficiency occurred during ESA therapy should be considered if hemoglobin levels do not increase after four weeks of therapy, and appropriate treatment administered. For patients treated with ESAs who have functional iron deficiency, IV iron is recommended as first-line treatment [37].

In fact, IV iron has been demonstrated to improve hemoglobin response to ESAs both in cancer as well as in dialysis patients [38].

An alternative way to modulate iron homeostasis may be represented by lactoferrin, which is a 78-kD cationic protein present in mammalian milk (where it was originally identified, hence the name), certain mucosal secretions, and polymorphonuclear (PMN) leukocytes playing an important role in host defense against infection and excessive inflammation [39]. In a paper carried out in a population of 148 advanced cancer patients undergoing chemotherapy we showed similar efficacy for oral lactoferrin in comparison to IV iron, combined with rHuEPO, for the treatment of cancer-related anemia. Moreover, the use of an orally administered compound gives further unquestionable advantages both in terms of patient compliance, because there is no need for hospitalization, and also in terms of cost savings. Indeed, it is well known that IV iron administration, aside from the general anaphylactic risks, also requires specifically trained medical staff and therapeutic support centers [40].

Blood transfusion therapy

The presence of mild to moderate anemia is generally associated an asymptomatic clinical picture, or mild clinical manifestations. This is due to the fact that the body provide compensation of the anemia that will maintain sufficient oxygen transport and perfusion into the tissues. Mechanisms that the body attempts to compensate for the anemia include increasing the flow of blood into tissues, the reduction of the viscosity of the blood, the increased unloading of oxygen within tissues, the elevated levels of 2,3 BPG, and the alteration of blood flow to target more important organs [41].

Therefore, clinical symptoms of anemia only appear

when the concentrations of hemoglobin become less than two-thirds of the normal values, which corresponds to less than 9-10 g/dl. Initial manifestations will be due to the elevation in cardiac output leading to the development of increasing fatigue, shortness of breath, and increased heart rate. Clinical manifestations will be more severe in the elderly where increased blood pressure and stroke volume might not be achieved due to dysfunctions in the cardiovascular system [42].

In these patients who develop clinical manifestations along with a severe decrease of hemoglobin levels, blood transfusion may be necessary. However, it is important to keep in mind that blood transfusion can be associated with transmission of serious infections like hepatitis C, and HIV. These infections were discovered in many patients who received blood transfusion during a bypass surgery. therefore, it is important to screen blood for common and serious infections before transfusion [43].

CONCLUSION:

Due to the continuing growth of the population of elderly individuals, the prevalence of anemia is continuously increasing which is leading to a huge burden on the community and the health care system. The main challenge in the management of anemia is the proper assessment and evaluation of the condition as this will determine later treatments and management plans. It is essential to determine the cause of anemia as treatment will usually target the underlying etiology. Most common causes of anemia in the elderly population include the presence of a chronic disease, the presence of a nutritional deficiency (most likely iron), or chronic kidney disease. Chronic blood loss is also an important cause that will eventually lead to the development of an iron deficiency anemia. In addition, chronic blood loss could be an indicator of serious illnesses like colorectal cancer, therefore, it should be taken seriously unless serious conditions have been ruled out. Treatment of anemia usually aims at achieving two outcomes: target the underlying cause, treat it (if possible), and improve blood quality. In cases where the underlying cause cannot be treated, or acute blood loss is present, blood transfusion can be indicated to give a rapid recovery of blood stores. Later, the use of recombinant erythropoietin will improve the general condition. In patients where blood transfusion is the only effective treatment, caution should be applied to prevent the development of associated adverse events which include infections and iron overload.

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