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Review Article

Issue of Anaemia in the Geriatric Patients: A Review on Haematological evaluation in Clinics

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Abstract

Anemia in the elderly (defined as people aged > 65 years) is common and increasing as the population ages. In older patients, anemia of any degree contributes significantly to morbidity and mortality and has a significant effect on the quality of life. Despite its clinical importance, anemia in the elderly is under-recognized and evidence-based guidelines on its management are lacking. Nonetheless, based on the WHO definition, studies have estimated that, in people over 65 years, the prevalence of anemia is 12% in those living in the community, 40% in those admitted to the hospital, and as high as 47% in nursing home residents. Commonly identified when the elderly are scheduled for elective surgical procedures. Anemia is a common condition in surgical patients and is independently associated with increased perioperative mortality. What constitutes appropriate evaluation and management for an elderly patient with anemia, and when to initiate a referral to a hematologist, are significant issues. In the present review we have collected the perspective on the different aspects of evaluation anaemia in the elderly patients and comment on the therapeutic management.

Keywords: Geriatric anaemia, Clinical evaluation, Therapy, blood transfusion.

Introduction

Anaemia is a common nutritional deficiency disorder or condition in person lacks enough healthy red blood cells to carry adequate oxygen in the entire body's tissues. Therefore, it can make people tired and weak which mostly affect the global public health in developing and developed countries with having major consequences for human health and their social and economic development.[1,2]

According to WHO (2004) reports, one third of the global populations (over 2 billion) are anaemic due to imbalance in their nutritious food intake & is now recognized as a risk factor for a number of adverse outcomes in the elderly, including hospitalization, morbidity, and mortality.[3] WHO estimates that even among the South Asian countries, India has the highest prevalence of anaemia. I addition more important fact is that about half of the global maternal & geriatric deaths are occur due to anaemia in South Asian countries like India & it commonly affected along with it covers about 80 per cent of the death ratio associated with them.[4]

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The elderly is an important demographic population that is growing rapidly[i] in the context of increasing prevalence of anemia with age.[3] With increasing recognition of the importance of anemia in the general population, guidelines have been published for the detection, evaluation, and management of anemia in medical and surgical patients.[5,6] However for elderly patients, attempts to identify suggested hemoglobin levels for management of anemia, including blood transfusion therapy, have been confounded by increased risks from anemia, along with additional co-morbidities. What constitutes an appropriate work-up for an elderly patient with anemia; and when to refer the patient to a hematologist, given the potentially large number of subjects involved, are significant costs-benefit issues.[7] In this review, we summarize our approach for management of anemia in the elderly, with a focus on transfusion therapy.

Types of anemia

The occurrence of anaemia is due to the various red cell defects such as production defect (aplastic anaemia), maturation defect (megaloblastic anaemia), defects in haemoglobin synthesis (iron deficiency anaemia), genetic defects of haemoglobin maturation (thalassaemia) or due to the synthesis of abnormal haemoglobin (haemoglobinopathies, sickle cell anaemia and thalassaemia) and physical loss of red cells (haemolytic anaemias).[8] This is a condition in which the body lacks the amount of red blood cells to keep up with the body's demand for oxygen. Understanding the different classifications can help to recognize the symptoms and also to avoid anaemia in the first place.Anemia in the elderly (age>65 years) is defined as a hemoglobin concentration below 12 gm/dl in women and below 13gm/dl in men. Older persons with anemia suffer disability, physical decline, and hospitalization at higher rates than those without anemia.[9,10] Anemia can never be considered normal in old age. There are 3 major classes of anemia namely Marrow production defects (Hypo-proliferation), Red cell maturation defects (Ineffective erythropoiesis) and Decreased redcell survival (Blood loss/ hemolysis).[11,12] Anemia of chronic disease and Myelodysplastic syndromes are seen more often in elderly. The most common causes of anemia in the elderly are chronic disease and iron deficiency. Vitamin B12 deficiency, folate deficiency, gastrointestinal bleeding and myelodysplastic syndrome are among other causes of anemia in the elderly. Serum ferritin is the most useful test to differentiate iron deficiency anemia from anemia of chronic disease. The serum methyl malonicacid level may be useful for diagnosis of vitamin B12 deficiency. Vitamin B12 deficiency is effectively treated with oral vitamin B12 supplementation. Folate deficiency is treated with 1 mg of folic acid daily.[13] Parameters such as serum albumin, transferrin, transferring saturation, cholesterol, cholinesterase, vitamin B12, folic acid, zinc, and absolute lymphocyte count are useful to assess the nutritional status.[13] More than two thirds of anemia in the elderly can be attributed to two major causes, nutritional deficiencies, and anemia of chronic disease. As many as 33% of geriatric anemia's remain unexplained and their pathogenesis remains speculative. Conjunctival pallor is a reliable sign and its presence should prompt clinician to order blood tests for anemia.[14] As per the NHANES III investigators, 10% of over 5000 community dwelling elderly subjects had anemia according to the WHO criteria. For the most part the anemia is mild, with hemoglobin levels infrequently less than 10 g/dL.[3] Nevertheless, this mild anemia has been associated with significant negative outcomes, including decreased physical performance, increased number of falls, increased frailty, decreased cognition, increased dementia, increased hospitalization, and increased mortality. This group further reported that about one third of these anemic patients have evidence of a nutritional deficiency, primarily that of iron; one third have chronic inflammation or chronic kidney disease (CKD); and one third have unexplained anemia.[3]

Pathophysiology of Geriatric anemia

A hyperinflammatory state is typical in anemia of inflammation (AI), CKD, and inflamed aging. This state is characterized by increased hepcidin production in the liver, resulting in a direct negative impact on erythropoiesis and increased iron retention in the reticuloendothelial system (RES). Moreover, production of EPO is insufficient in response to anemia, and EPO response in the erythropoiesis is blunted. A further hallmark in the pathogenesis of AI is the increased phagocytosis of aging erythrocytes (eryptosis). Clonal disorders in leukocytes increase the risk of developing cardiovascular complications and anemia. This association may be caused by the promotion of inflammatory processes. Plus signs symbolize stimulation, and minus signs inhibition (Fig. 1).

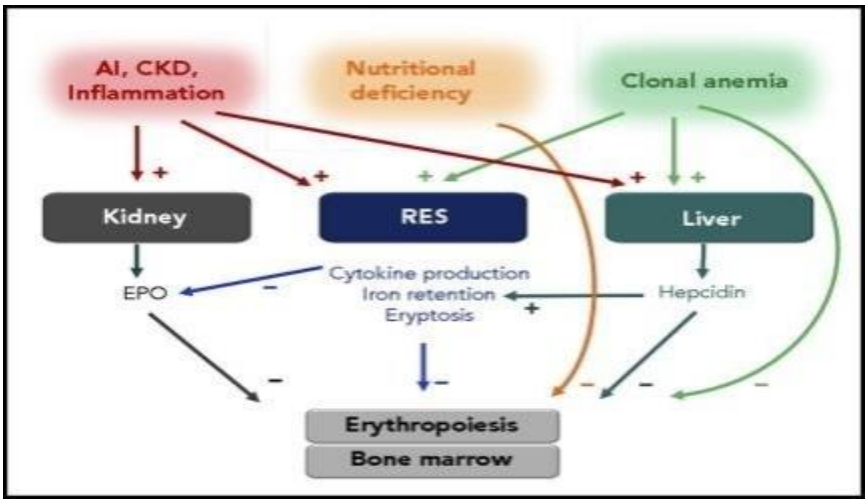

Fig. 1. Possible mechanism of anemia in Geriatric[14]

Diagnostic criteria

Evaluation of geriatric anemia

Geriatric anemia is commonly identified in patient by using elective surgical procedures. Anemia is a common condition in surgical patients and is independently associated with increased perioperative mortality. Regular approaches to evaluating a patient with anemia are the mean corpuscular volume (MCV) followed by biochemical analysis.[15] The MCV has been shown to add value to the red cell distribution width (RDW) for evaluation of macrocytosis. However, for microcytic anemias, MCV is of less value, particularly for patients with iron deficiency who have comorbidities. However, the MCV is normal in 70% of patients with anemia of inflammation limited iron delivery to red cell precursors as indicated by the low transferrin saturation.[16] This overlap of these two common causalities of anemia (iron deficiency and inflammation) has made the use of the traditional markers: MCV, transferrin saturation, and ferritin, difficult to interpret in routine practice. An algorithm for the evaluation and management of anemia in the elderly is presented in Fig. 2. Iron-restricted erythropoiesis can cause anemia due to an absolute iron deficiency, iron sequestration which is mediated by hepcidin, and/or a functional iron deficiency due to the erythropoietin-stimulated erythropoiesis.[17] The evaluation of anemia must also consider unexpected diagnoses including CKD or occult malignancy. If absolute iron deficiency is diagnosed, in the elderly postmenopausal population it is mandatory to rule out gastrointestinal (GI) pathology, including malignancy as a source of chronic blood loss.

Referral to a gastroenterologist may be the most effective way to proceed. However, in one-third to two-thirds of such patients, work-up of the GI tract is negative. Serum creatinine and GFR must be determined in order to evaluate for CKD, in which case referral to a nephrologist may be appropriate. The suggested cut-off of glomerular filtration rate (GFR) careful history for alcohol use/abuse particularly in patients with an MCV > 100 may be in order contributing either to poor marrow reserve or folate deficiency in the elderly. An early study by Cash and Sears of 90 patients (mean age 50.9 6 16.5, not confined to elderly individuals) with anemia of chronic disease observed that there was a broader spectrum of associated diseases with ACD than had previously been recognized. A more recent 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; whereas testosterone levels were lower in men and erythropoietin levels were inappropriately low for the degree of anemia. The diagnosis of UAE is usually considered when other causes of anemia in the elderly have been eliminated. The diagnosis of UAE is based on the findings of a

hypoproliferative anemia: a low reticulocyte index and an inadequate erythropoietin level for the degree of anemia. The management of these patients is a serious and recurrent issue, since in the absence of an etiology there is no proven efficacious intervention. When such patients are symptomatic, when they find themselves in clinical situations involving blood loss, or when surgical intervention is required, consideration of transfusion therapy is necessary, as described below.

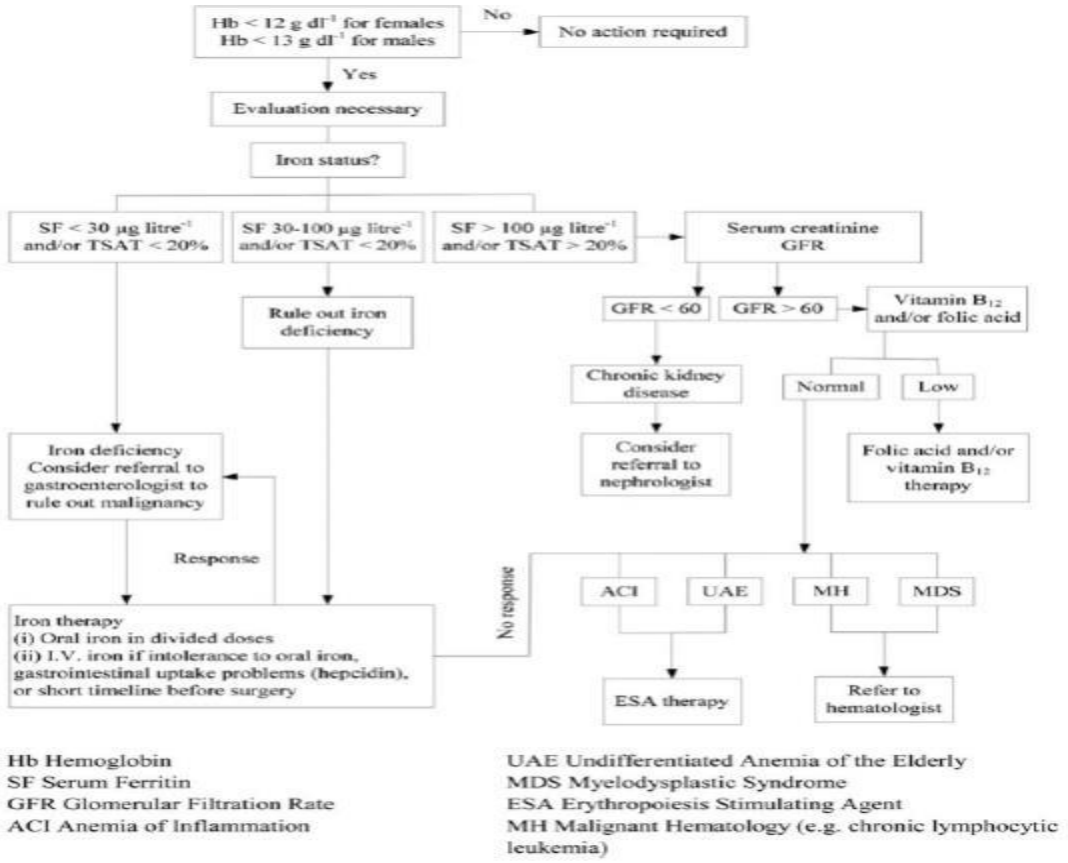

Fig 2: Evaluation & Management of Geriatric anemia[18]

(Fig 2 Blurred-Please change)

Diagnostic aspects

Primary laboratory evaluation in older anemic patients should include basic parameters including Hb, differential blood count, MCV, mean corpuscular hemoglobin, reticulocyte count, ferritin, reticulocyte Hb, TSAT, EPO level, CRP, fibrinogen, creatinine/glomerular filtration rate,vitamin B_{12}, serum folate, copper, thyrotropin, lactate dehydrogenase, haptoglobin, alanine aminotransferase/aspartate aminotransferase, and serum electrophoresis. In quite a number of cases, this profile will help identify and classify nutritional deficiency including iron-deficient anemia, AI, and CKD. Depending on the clinical evaluation, more detailed investigations may be needed including gastro- and colonoscopy and ultrasound of the abdomen and kidney. BM aspiration and biopsy are mandatory to exclude hematologic disorders including MDS and to make an appropriate diagnosis, especially when additional blood count abnormalities or other signs of a clonal hematologic disease are found. These diagnostic procedures including BM evaluation should, however, be discussed in light of the burden of the procedure and weighed against the possible therapeutic

consequences of the suspected diagnosis as well as life expectancy and burden of anemia. The authors feel the patient should have a life expectancy of minimum 3 months in order to justify BM aspiration in an anemic elderly patient.

In those with unclear results molecular, cytogenetic, and/or flow cytometry studies may help reach the conclusion that the patient is suffering from a clonal BM disorder such as MDS. In such studies, detection of clonality of myeloid cells may cause a change in the diagnosis, for example from ICUS to CCUS or even to MDS.[19] There are a number of other complex conditions and pitfalls that may pose diagnostic problems in elderly patients, especially those who suffer from comorbidities. For example, it may be difficult to assess the extent of iron deficiency in patients suffering from inflammatory bowel disease and pronounced inflammatory bowel disease–related inflammation. In these cases, soluble transferrin receptor (sTfR), the sTfR/log ferritin index, and serum hepcidin may assist in estimating the degree of iron deficiency. An index above a certain cutoff level indicates the presence of a true iron deficiency that may be overseen in an inflammatory state when using ferritin and TSAT levels only. Specific cutoff levels have been published. A ratio of <1 suggests AI, whereas a ratio of >2 suggests absolute iron deficiency coexisting with AI.[20] Yet, it is important to understand that sTfR assays are not standardized, and therefore, a cutoff level for the sTfR/log ferritin index has to be established by each laboratory individually, depending on the sTfR assay.[21] Other parameters like reticulocyte Hb content and percentage of hypochromic erythrocytes have proved to be informative to predict the response rate to iron therapy in CKD patients.[22-23]

Therapeutic options

Before establishing a treatment plan, the primary diagnosis and accompanying diseases with emphasis on treatable disorders should be properly defined. As mentioned before, often several causes contribute to anemia in the elderly. Then, optimal age-adjusted therapy is introduced, with recognition of potential side effects and impact on QoL. Even a weekly referral (transport burden) for injections may already interfere with QoL in frail patients. Whenever possible, the primary goal is to treat and thus eliminate the underlying disease and thereby the etiology of anemia.

In most patients suffering from true ID, oral iron substitution seems to be sufficient.[24] Moreover, in recent years new oral iron formulations like ferric maltol and Sucrosomial Iron showing higher efficacy and fewer side effects have been approved, thus further reducing the need for intravenous iron. Yet, sometimes oral application in the elderly is not effective because of reduced uptake in the GI tract, impaired compliance, and/or an inflammatory state leading to decreased iron utilization.[25,26] In this situation, when oral iron does not ameliorate anemia, IV iron therapy may be a valuable alternative. Actually, a number of IV iron formulations are available including iron sucrose, ferric gluconate, and ferumoxytol. Therefore, we are of the opinion that IV iron supplementation should be recommended when oral iron preparations are not tolerated, in patients nonadherent to oral iron substitution, in case of ongoing blood loss, or if iron uptake in the GI tract is insufficient.

Erythropoiesis-stimulating agents (ESAs) are so far registered for the treatment of anemia in CKD and in European Union countries in patients with MDS. Data on application of ESAs in other subtypes of anemia are limited. Nevertheless, 1 study suggested that EPO may be beneficial in a patient cohort of age 65 and older African American women with no obvious explanation for the existing anemia.[27] In that study, ESAs significantly increased Hb levels and also patients' QoL. Yet, considering studies reporting a reduced EPO response in a large portion of UA patients, larger studies are definitely needed to support the idea of ESA therapy in UA patients.[28] In general, the risk for thromboembolic complications increases at higher Hb levels, so that the current recommendation is to maintain Hb levels between 9 and 11.5 g/dL. Blood transfusions are the first and most effective option for the treatment of elderly patients with severe, symptomatic anemia. Although no specific cutoff level is available for Hb, elderly anemic patients should always be transfused with recognition of comorbidities and an adequate oxygen supply that needs to be maintained. Transfusion numbers and frequency in the individual patient have to be based on many different factors and the overall situation in each case. In those with severe cardiovascular disorders, blood should be transfused more slowly and on a unit-by- unit basis, and Hb levels should be kept above 9 or even 10 g/dL in these patients.

Thanks to a better understanding of mechanisms regulating erythropoiesis, new drugs are currently being developed such as hepcidin inhibitors (Table 4). Currently, these drugs are mainly developed for anemia in CKD and cancer patients. However, they may be a future therapeutic approach for a defined group of elderly patients. Another group of agents are the hypoxia inducible factor (HIF)–prolyl hydroxylase inhibitors. Especially older patients with low endogenous EPO levels may benefit from these drugs. Yet, persons at advanced age may be more vulnerable to HIF stabilization. Finally, activin type II receptor agonists are currently being investigated in patients with MDS and CKD and might present a future option for the treatment of anemia at advanced age. As sufficient clinical data are not yet available, these drugs still await final approval.

Conclusion

Anemia in the elderly (defined as people aged > 65 years) is common and increasing as the population ages. In older patients, anemia of any degree contributes significantly to morbidity and mortality and has a significant effect on the quality of life. Despite its clinical importance, anemia in the elderly is under-recognized and evidence-based guidelines on its management are lacking. In this review we support the notion that Each patient must be evaluated individually, and patient-specific anaemia management strategies be employed.

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