A narrative review of anaemia in the elderly in a primary care setting

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ABSTRACT

Background

Anaemia in the elderly is a common finding. Its causes are multiple and its management will depend on the underlying cause.

Objective

The aim of this article is to review the latest literature on anaemia in the elderly with a specific focus on the primary care setting.

Method

A search for review articles using the MeSH words "Elderly" OR "Older People" OR "Older Persons" or "Age 65+" AND "anaemia" OR "anemia" AND "primary care" was carried out on Medline EBSCO for articles in English published between 2012 and 2022. The PRISMA guideline was followed in the selection of articles to ensure research rigour. The initial search yielded 931 articles which were finally reduced to 17 articles.

Results

The topics discussed in the selected articles were varied. The vast majority gave a broad overview of anaemia. Others focused on specific aspects of anaemia like treatment, iron deficiency anaemia, autoimmune hemolytic anaemia, chronic kidney disease, the role of nutrition and the inflammatory pathways leading to anaemia.

Discussion

The authors focused on themes that came out of the selected papers, namely: symptoms and significance, causes, approach to investigations and therapeutic options.

Conclusion

Anaemia is a common finding in the elderly population and it should not be considered as a normal aging process. Proper investigation can frequently elucidate the cause and provide adequate treatment.

Keywords

Anaemia, elderly, older people, primary care

Abbreviations and acronyms used in the article

AA	Aplastic anaemia
AHA	Autoimmune haemolytic anaemia
AI	Anaemia of inflammation
CCUS	Clonal cytopenia of undetermined significance
CHIP	Clonal haematopoiesis of indeterminate potential
CKD	Chronic kidney disease
DAT	Direct antiglobulin test
EPO	Erythropoietin
GI	Gastrointestinal
Hgb	Haemoglobin
HIV	Human immunodeficiency virus
ICUS-A	Idiopathic cytopenia of unknown significance with anaemia
IDA	Iron deficiency anaemia
MCV	Mean corpuscular volume
MDS	Myelodysplastic syndrome
TACO	Transfusion associated circulatory overload
TRALI	Transfusion related acute lung injury
UA	Unexplained anaemia

INTRODUCTION

Anaemia is defined as a reduced oxygen carrying capacity of the body due to a decrease in the red blood cells or the haemoglobin (Hgb) concentration. In 1968, the WHO study group published two cut-offs to define anaemia, a Hgb <12gd/L in females and <13gd/L in males. Even if the cohort used to measure these two values consisted of healthy young Caucasians, excluding elderly over 65 years of age, these measures are still used to this day (World Health Organization, 1968).

In the elderly, anaemia is extremely common, probably because other diseases are also more prevalent with increasing age. Despite this, Guralnik et al. (2004) reasoned that anaemia should not be considered as an inevitable consequence of aging and it may be useful to identify it and any underlying cause as many treatment options are available. Causes are varied and, in some patients, two or more pathologies may contribute to their low Hgb level. Management will depend on the underlying cause, the severity, as well as the patient's general condition.

The aim of this review was to evaluate the latest evidence on anaemia in the elderly and summarise the findings.

METHOD

In this narrative review the authors sought to evaluate the literature available on the topic of anaemia in the elderly with a particular focus on the primary care setting. This will help to identify any gaps in knowledge. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline was used to ensure rigour in research (Page et al., 2021).

Study designs

This narrative review included systematic reviews published over the past 10 years (2012-2022), in the English language. For an article to be included in the authors' selection, the article needed to discuss anaemia in the elderly.

The authors searched the Medline EBSCO database for relevant articles. Each author performed a separate search, and any disagreements were resolved by consensus. The search was restricted to one major database to keep this review manageable and because of the resources available.

The following search words were used: "Elderly" OR "Older People" OR "Older Persons" or "Age 65+" AND "anaemia" OR "anemia" AND "primary care".

The following filters were applied: English language, age over 65, full text available and systematic review.

The initial search yielded 931 articles. The title of each article was then scanned for appropriateness and for duplicate articles. This search resulted in 842 articles being rejected leaving 89 articles for further evaluation.

The abstract of each remaining article was then read. This process resulted in the elimination of a further 65 articles with the remaining 24 articles being selected for this review.

Review of the full text of these articles eliminated another 5 articles. A further 2 articles were eliminated as their full text was not available. Thus, 17 articles were selected this review. Table 1 lists these articles. Figure 1 graphically explains the selection process.

Table 1 - The articles selected for this review

	Authors	Date of publication	Title
1	Stauder, R., Valent, P. and Theurl, I.	2018	Anemia at older age: etiologies, clinical implications, and management
2	Andres, E. et al.	2013	Anemia in elderly patients: new insight into an old disorder.
3	Katsumi, A. et al.	2021	Anemia in older adults as a geriatric syndrome: A review.
4	Lanier, J.B. et al.	2018	Anemia in Older Adults.
5	Girelli, D., Marchi, G. and Camaschella C.	2018	Anemia in the Elderly.
6	Halawi, R., Maukhadder, H. and Taher, A.	2017	Anemia in the elderly: a consequence of aging?
7	Röhrig, G	2016	Anemia in the frail, elderly patient.
8	Gadò, K. et al.	2022	Anemia of geriatric patients.
9	Barcellini, W., Fattizzo, B. and Cortelazzi, A.	2018	Autoimmune hemolytic anemia, autoimmune neutropenia and aplastic anemia in the elderly.
10	Goodnough, L.T. and Schrier, S.L.	2014	Evaluation and management of anemia in the elderly.
11	Tavenier, J. and Leng, S.X.	2019	Inflammatory Pathways to Anemia in the Frail Elderly.
12	Joosten, E.	2018	Iron defiency anemia in older audults: A review.
13	Musio, F.	2019	Kidney Disease and Anemia in Elderly Patients.
14	Bianchi, V.E.	2016	Role of nutrition on anemia in elderly.
15	Silay, K. et al.	2015	The status of iron absorption in older patients with iron deficiency anemia.
16	Busti, F. et al.	2019	Treatement options for anemia in the elderly.
17	Alvarez-Payares, J.C. et al.	2021	Unexplained Anemia in the Elderly.

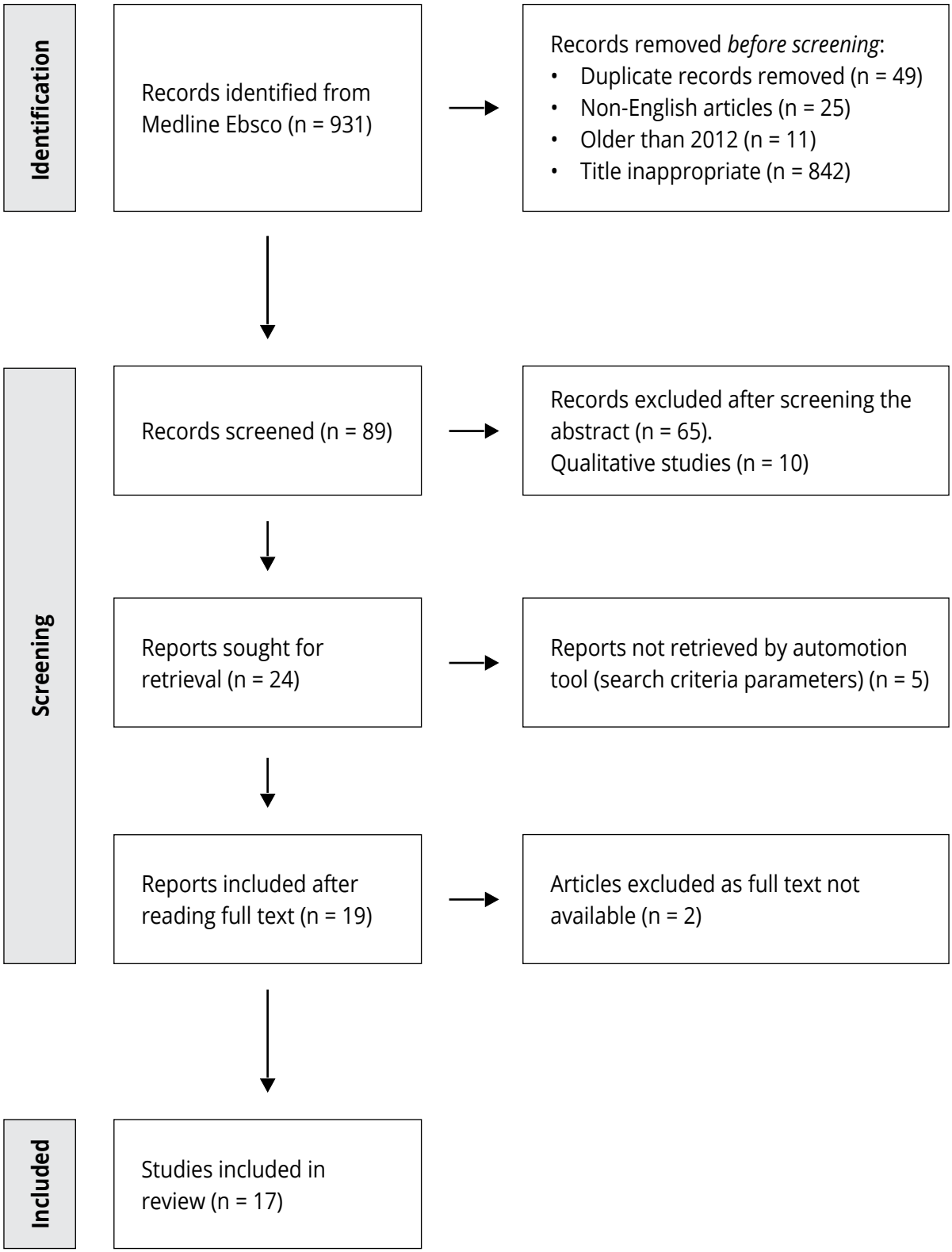

Figure 1: Selection process flowchart

RESULTS

Nine of the retrieved articles presented a general overview of presentation, diagnosis and management of anaemia in the elderly population (Andrès et al., 2013; Goodnough and Schrier, 2014; Röhrig, 2016; Halawi, Moukhadder and Taher, 2017; Stauder, Valent and Theurl, 2018; Girelli, Marchi and Camaschella, 2018; Lanier, Park and Callahan, 2018; Katsumi et al., 2021; and Gadó et al., 2022). Treatment of anaemia was the main discussion point in Busti et al. (2019). Joosten (2018) and Silay et al. (2015) focus on iron deficiency anaemia. Unexplained anaemia in the elderly was the subject reviewed by Alvarez-Payares et al. (2021). Bianchi (2016) discussed the role of nutrition in the development of anaemia in the elderly, whereas Musio (2019) explored the role of chronic kidney disease (CKD) in the development of anaemia in the elderly. Tavenier and Lang (2019) discussed the inflammatory pathways of anaemia in this age group and Barcellini, Fattizzo and Cortelezzi (2018) explore autoimmune hemolytic anaemia in the elderly.

Following the thematic analysis, the following themes were identified:

1. Symptoms and significance of anemia in the elderly
2. Causes of anemia in the elderly
3. Approach to investigation of anemia in the elderly
4. Therapeutic options.

DISCUSSION

The discussion will follow the themes identified in the thematic analysis.

1. Symptoms and significance of anaemia in the elderly

Anaemia, even when mild, may significantly affect quality of life in the elderly, both in physical and cognitive faculties. Many studies observed that, apart from being associated with frequent hospitalization and prolonged hospital stay as well as cardiovascular events, falls, cognitive impairment and mental well-being, it is also a marker for increased morbidity and mortality (Stauder, Valent and Theurl, 2018; Andrès et al., 2012).

Most elderly patients will often have only minor Hgb reductions and therefore many will be asymptomatic. The commonly associated symptoms of anaemia, such as fatigue, exertional dyspnoea and tachycardia, will be present in varying degrees of severity in this cohort of patients. Additionally, other subtle signs and symptoms might prevail, and these include confusion, apathy and falls (Andrès et al., 2012).

The patients might also complain of symptoms related to the pathogenesis of the disease. Patients with haematinic deficiencies can present with hair and nail changes such as hair loss and leukonychia seen in iron deficiency anaemia (IDA) and glossitis in cobalamin (B_{12}) and folate (B_9) deficiency (Andrès et al., 2012). In the elderly, IDA has been linked to restless legs syndrome (Joosten, 2018). Very rarely, Vitamin B_{12} deficiency presents with neurological symptoms. Patients with anaemia arising from bone marrow disorders may complain of recurrent infections associated with low or dysfunctional leukocytes and bleeding problems due to a low platelet count (Gadó et al., 2022).

2. Causes of anaemia in the elderly

There are a multitude of possible causes, and an easy classification would be according to the mean corpuscular volume (MCV). Table 2 gives a comprehensive list of common causes of anaemia in the elderly based on the MCV and the relevant investigations needed. Investigations can be guided by the MCV but it is important to consider that dual pathology may be present and patients may have a dimorphic picture.

Table 2 - Classification showing different causes of anaemia in the elderly based on the mean corpuscular volume (MCV) and suggested investigations.

	Possible causes	Investigations suggested	Other specialist investigations to consider
Microcytric <80fL	• Iron deficiency anaemia - chronic blood loss from GI or urinary tract, nutritional, malabsorption • Haemoglobinopathies such as thalassaemia	• Blood film • Ferritin, iron profile • Haemoglobinopathy screen • Coeliac screen	• If IDA confirmed, consider endoscopy study +/- ultrasound abdomen +/- capsule endoscopy
Normocytic 80-100fL	• Chronic kidney disease • Low EPO levels • Haemolysis (hypersplenism, mechanical valves, autoimmune - extravascular / intravascular) • Bone marrow infiltration causing reduced production of red cells. May include cancers such as lymphoma, multiple myeloma, breast cancer metastasis or infection such as HIV, parvovirus • Anaemia of inflammation	• Blood film • Reticulocyte count • Renal profile • C-reactive protein, erythrocyte sedimentation rate • Antinuclear antibody and autoimmune screen • Serum protein electrophoresis and immunoglobulins; serum calcium	• Serum EPO levels • Ultrasound abdomen and kidneys • Lactate dehydrogenase • Serum haptoglobin and direct antiglobulin test • Bone marrow aspirate and trephine biopsy • Molecular, cytogenetic and flow cytometry • Virology screen
Macrocytic >100fL	• Folate deficiency • Vitamin B_{12} deficiency • Myelodysplastic syndromes • Haemolysis • Liver disease • Alcohol misuse - associated with malnutrition and liver disease • Drug-included - chemotherapeudic agents such as hydroxyurea or antimetabolites such as methotrexate or phenytoin (these cause folate deficiency) • Thyroid disorders	• Blood film • Haematinic screen - vitamin B_{12} and folate • Liver profile • Thyroid function tests • Coeliac screen	• Anti-intrinsic factor antibody, anti-parietal cell antibody

With regards to the nutritional anaemias, IDA is usually the most common (Silay et al., 2015). Identifying it is beneficial as various treatments are available and in less frail patients it might be appropriate to search for a possible cause of occult blood loss. Commonly, this would be bleeding from the gastrointestinal (GI) tract such as peptic ulceration, gastritis, polyps and cancers. Concerning folate or vitamin B_{12} deficiency, malabsorption in the elderly is usually more often due to age-related decreased GI absorption and polypharmacy, rather than coeliac, pernicious anaemia or inflammatory bowel disease (Stauder, Valent and Theurl, 2018). Poor diet may be related to social isolation, decreased cognitive function and financial circumstances. The Food-Cobalamin Malabsorption syndrome, associated with Vitamin B_{12} deficiency, is the failure of cobalamin to be released from food or transport proteins in the setting of hypochlorhydria. This occurs in atrophic gastritis and chronic gastritis, *Helicobacter pylori* infections as well as drugs such as omeprazole and metformin, all extremely common in the elderly (Halawi, Moukhadder and Taher, 2017).

Another significant cause of anaemia in the elderly is anaemia of chronic disease or as it is now known as anaemia of inflammation (AI). This is extremely common and various interrelated mechanisms are believed to be responsible. One example would be the decreased proliferation of red cell precursors in the presence of increased inflammatory cytokines, mostly IL-1, IL-6 and tumour necrosis factor (Tavenier and Lang, 2019). Reduced production of erythropoietin (EPO), together with a diminished response to it, occurs in AI and this can occur in the absence of CKD. Moreover, the protein hepcidin decreases iron absorption and release from macrophages. Hepcidin is an acute phase reactant and is increased in AI, cancer patients, chronic infections and autoimmune conditions (Girelli, Marchi, and Camaschella, 2018). This statement also holds true for the protein ferritin, which is often found to be increased in inflammatory conditions. A third mechanism causing anaemia related to inflammation is by means of increased eryptosis, which is the death of red cells. Diseases in which eryptosis is common, such as diabetes and congestive heart failure, are also extremely prevalent in the elderly. The term inflammaging has been coined to describe the generalized, low-grade, chronic inflammation that occurs in association with aging (Röhrig, 2016). Anaemia in the setting of CKD arises not solely due to decreased EPO production but also because of background chronic inflammation, malnutrition and iron deficiency (Musio, 2019).

Haematological disorders are uncommon causes of anaemia but some do occur with increasing incidence in the elderly. A classic example is myelodysplastic syndrome (MDS) which is primarily considered to be a disease of the elderly. It comprises of a group of heterogenous disorders featuring dysplasia and ineffective haematopoeisis in one or more of the bone marrow cell lines. Multiple myeloma and chronic lymphocytic leukaemia are two other haematological disorders which are especially found in older patients (Gadó et al., 2022).

With age, antibodies directed against self are found with increased frequency, most often without developing into an established clinical disorder. Two autoimmune mechanisms by which anaemia can result include autoimmune haemolytic anaemia (AHA) and aplastic anaemia (AA). AHA is diagnosed by means of the direct antiglobulin test (DAT) and is classified as warm, cold or mixed depending on the temperature at which the auto-antibody against red cells is active. It can be primary but in most cases it is secondary to solid or haematological cancers, drugs and infections (Barcellini, Fattizzo and Cortelezzi, 2018). In AA the autoantibodies are directed toward haemtopoeitic stem cells. Intravascular haemolysis is also observed in patients with prosthetic valves and stents. Amongst the complications of haemolysis which include gallstones and kidney disease, the most common are thrombosis and infections, especially in asplenic patients. Identifying haemolysis at an early stage may avoid these (Barcellini, Fattizzo and Cortelezzi, 2018).

When extensive investigations do not reveal a cause for their anaemia, patients are often labelled as having unexplained anaemia (UA). Alvarez-Payares et al. (2021) described how bone marrow tests in elderly patients often show somatic mutations in their red blood cells leading to clonal hematopoiesis. In patients with no cytopenias this is termed as clonal hematopoiesis of indeterminate potential (CHIP). However, these mutations often cause cytopenias and then these patients will be diagnosed to have either clonal cytopenia of undetermined significance (CCUS) or MDS. Patients who are found to have anaemia without molecular abnormalities are diagnosed with idiopathic cytopenia of unknown significance with anaemia (ICUS-A). CHIP and CCUS may develop into MDS, which may or may not predispose to acute myeloid leukaemia (Alvarez-Payares et al., 2021). There is also a great degree of clinical overlap between paroxysmal nocturnal haemoglobinuria, AA and MDS (Barcellini, Fattizzo and Cortelezzi, 2018).

Anaemia can also arise in the context of pancytopenia secondary to bone marrow suppression which can occur with infections such as human immunodeficiency virus (HIV), tuberculosis, leischmaniasis, Parvovirus B19, drugs and infiltration with malignancy (Barcellini, Fattizzo and Cortelezzi, 2018).

In their review, Katsumi et al., (2021) mention low testosterone levels and trace element deficiencies as a possible mechanism of unexplained anaemia. They describe how copper deficiency can lead to a clinical picture similar to MDS. It can occur after gastric surgery or in patients on zinc supplements, which impairs copper absorption. Girelli, Marchi and Camaschella (2018) claim that Vitamin D deficiency was also found to be related to low Hgb levels. In some patients, even after extensive investigation, the cause of the anaemia still remains unclear.

3. Approach to investigation of anaemia in the elderly

The assessment of an elderly patient with anaemia should start with a thorough history and examination. This entails exploring severity of symptoms of anaemia, looking for a possible underlying cause, determining the functional status and frailty of the patient as well as the social background and support. A good history may reveal alarm symptoms such as melaena, weight loss, bone pains pointing towards a potential malignancy or a possible malabsorption or malnutrition problem. Examination is crucial to identify possibly haematological causes such as splenomegaly and also to detect any chronic problems such as chronic infections or autoimmune diseases.

Investigation of anaemia starts with a full blood count which includes a differential count, MCV and reticulocyte count. It is essential to check renal, liver and thyroid function tests and a haematinic screen – serum folate, serum vitamin B_{12}, ferritin and iron profile.

AI is characterized by a low serum iron and low iron-binding capacity associated with an elevated ferritin whilst IDA is indicated when the serum iron and transferrin saturation are low whilst the iron-binding capacity is high. Checking ferritin levels is only useful if the result is low because this effectively confirms IDA. Sometimes IDA and AI may coexist, complicating the interpretation of the iron studies. If there is microcytic anaemia without evidence of iron deficiency, this should prompt investigation for a haemoglobinopathy.

Depending on the results of these basic tests, further investigations may be useful, and these might include ultrasound of the abdomen and kidneys. In cases of nutritional anaemias, check for *Helicobacter pylori* and coeliac screen, whilst other patients may benefit from a full GI workup. Serum protein electrophoresis, serum calcium and x-rays looking for lytic lesions will help in the evaluation of multiple myeloma or other plasma cell dyscrasias. If the history is suggestive, one could consider an autoimmune screen or virology

tests (HIV and hepatitis screen). All cases of haemolysis have an increased unconjugated bilirubin, an increased reticulocyte count, increased lactate dehydrogenase levels whilst haptoglobin levels are decreased. A positive DAT is indicative of an autoimmune process for the haemolysis. In some instances, bone marrow studies may be indicated but many authors agree that because of the invasiveness of the tests, these are only undertaken if the life expectancy of the patient is expected to be more than three months (Stauder, Valent and Theurl, 2018; Alvarez-Payares et al., 2021).

4. Therapeutic options

Management of anaemia in the elderly is challenging. Many therapeutic options are available, but treatment has to be balanced with the clinical situation and frailty of the patient, the impact on quality of life and the side effects of treatment.

In cases of IDA, patients should be advised to consume more red meat, poultry and fish because these are excellent sources of heme iron. Heme iron is better absorbed than ferrous iron and is associated with fewer side effects. For therapeutic oral supplementation, many preparations with ferrous iron are available and are cheap, effective and safe. There are solid and liquid preparations with prolonged or quick release forms, with ferrous sulphate and ferrous gluconate being the most prescribed as both have excellent bioavailability. Treatment should be continued for at least three months after correction of anaemia. Oral iron treatment is often hampered by the frequent GI side effects which range from constipation, black hard stools, abdominal pain to nausea and vomiting. This may lead to noncompliance. Anti-acids may decrease iron absorption as do the tannins and polyphenols in tea and coffee (Andrès et al., 2012). Patients should be instructed to take oral iron with orange juice as Vitamin C improves absorption (Bianchi, 2016). Intravenous iron has the benefit that the total dose of iron needed can be calculated and replenished in a single or a few doses. It is safe but can be associated with anaphylaxis and increased susceptibility to infections. It is the preferred treatment of iron replacement in patients with CKD, inflammatory bowel disease and the elderly with problems of malabsorption (Silay et al., 2015; Röhrig, 2016).

With regards to the other nutritional deficiency anaemias, folic acid and vitamin B_{12} are prescribed as oral preparations. In patients with malabsorption, inflammatory bowel disease and pernicious anaemia, Vitamin B_{12} can be administered as an intramuscular injection (Lanier, Park and Callahan, 2018).

Erythopoesis-stimulating agents such as recombinant human EPO are typically used in patients with CKD but are increasingly used in MDS and few selected cases of unexplained anaemia (Goodnough and Schrier, 2014). EPO can exacerbate hypertension and, very rarely, worsen the anaemia by causing pure red cell aplasia. An aim for Hgb between 10 and 11.5g/dL is ideal as levels above 13g/dL have been associated with increased risk of stroke, thrombosis and cardiovascular events (Halawi, Moukhadder and Taher, 2017).

Blood transfusions are usually reserved for the immediate treatment of patients with severe, symptomatic anaemia or those who are critically ill. Decisions to transfuse should not be based solely on the Hgb level but also on symptoms and patient factors. The single-unit transfusion policy is suggested by Busti et al. (2019) and consists of transfusing one unit of red cells and then assessing the patient for improvement of anaemia symptoms and any complications. Adverse effects include transfusion-associated circulatory overload (TACO), transfusion-related acute lung injury (TRALI), iron buildup and increased risk of transmitting infections.

In cases of haemolysis, the treatment is directed towards identifying and treating any underlying cause. Steroids and rituximab are the mainstay of treatment in cases of warm AHA whilst rituximab and transfusions are applied in cold AHA. Management of AA may

consist of immunosuppressive treatment with a combination of ciclosporin and horse-derived antilymphocyte globulin or in the case of frail patients, single agent ciclosporin (Barcellini, Fattizzo and Cortelezzi, 2018).

Treatment of MDS consists mainly of supportive transfusions, iron-chelating agents and EPO injections (Halawi, Moukhadder and Taher, 2017). A small number of patients are found to have deletion of the 5q chromosome, and this is usually associated with good prognosis. These patients may benefit from oral thalidomide or lenalidomide. In other patients with MDS the hypomethylating agent azacytidine was found to improve quality of life. Only a few selected patients with an excellent performance status are considered for allogeneic stem cell transplantation (Gadó et al., 2022).

CONCLUSION

Despite being common, anaemia presenting in old age should not be disregarded as a normal consequence of aging. Investigation and management can be challenging especially if undertaken in the community. However, since many treatments are available, correcting the anaemia will improve the quality of life of elderly patients. Many drugs are still being investigated for the treatment of anaemia, particularly for myelodysplasia and anaemia of chronic disease. What is evident when reading the literature is the need for more research in this group of patients.

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