INTRODUCTION:

Anaemia is common in the elderly and its prevalence increases with age. Using World Health Organization criteria (haemoglobin of less than 12 gm per dL in female and less than 13 gm per dL in male) for the prevalence of anaemia in the elderly has been found to range from 8 to 44 percent, with highest prevalence in man of 85 years and older. In 2004, the American Society of Haematology conducted a special forum to discuss the problem of anaemia in the elderly as it is considered a public health crisis in haematology. It is estimated that more than 3 million people in the US aged 65 and older have anaemia. In various studies the prevalence is reported as 10 to 45% of elderly population. Generally the prevalence of anaemia increases with each decade. It is hence a common growing health problem.

The increased incidence of anaemia with aging has led to speculation that lower haemoglobin levels may be a normal consequence of aging. However, there are at least two reasons for considering anaemia in the elderly as a sign of disease. First, most older people maintain a normal red cell count, haemoglobin and haematocrit. Second, in most elderly patients an underling cause of anemia is found for haemoglobin of less than 12 g per dL.

CAUSES OF ANAEMIA IN ELDERLY:

Anaemia in the elderly is more commonly observed than appreciated and is often multifactorial, with multiple factors contributing to the problem in an individual patient. Dr. Artz stated that—“in elderly persons the etiology of anaemia differs sufficiently from younger adults to warrant considering anaemia in elderly person as a distinct entity. Nutritional deficiencies account for approximately 34% of cases of anaemia in elderly, while anaemia of chronic disease with or without renal insufficiency, accounted for an additional 33% as many as 33% of geriatric anaemias remain unexplained, and their pathogenesis remain speculative. More than to two third of anaemia in the elderly can be attributed to two major causes, (1) nutritional deficiencies and (2) anaemia of chronic diseases. Following are some of the possible causes of anaemia in elderly —

Deficiency Disorders —
- Folic acid deficiency anaemia.
- Iron deficiency anaemia.

PC Bhattacharyya,
Manabendra Nayak, Guwahati

- Malabsorption syndrome.
- B12 malabsorption
- Allergic, Collagen, Auto-immune disorders
- Rheumatoid arthritis
- Sprue (gluten enteropathy ).
- SLE.
- Vasculitis.
- Polymyalgia rheumatica.
- Haemolytic anaemia.
- Auto-immune arteritis.
- Hereditary, Familial Genetic Disorders –
- Sickle cell trait.
- Sickle cell anaemia.
- Hereditary spherocytosis.

Endocrine Disorder –
- Hypothyroidism (myxedema).
- Panhypopituitarism.
- Anaemia with endocrinopathies.
- Hyperinsulinemia.

Drugs –
- Drug induced gastritis.

Poisoning (specific agent) –
- Chronic alcoholism.

Hierarchical major groups –
- Blood / Bone marrow disorders.

Reference to Organ System –
• Peptic ulcer disease.
• Anaemia of chronic disease.
• Bone marrow failure.
• Chronic blood loss.
• Anaemia in CKD
• Refractory anaemia.
• Myelophthsisic anaemia.
• Pernicious anaemia.

Neoplastic Disorders.
Surgical complications.
Infectious Disorders

Summary of the common causes of Anaemia in the Elderly

<table>
<thead>
<tr>
<th>CAUSE OF ANEMIA</th>
<th>PERCENTAGE OF CASES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia of chronic disease</td>
<td>30 to 45</td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>15 to 30</td>
</tr>
<tr>
<td>Posthemorrhagic</td>
<td>5 to 10</td>
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<tr>
<td>Vitamin B₁₂ and folate deficiency</td>
<td>5 to 10</td>
</tr>
<tr>
<td>Chronic leukemia or lymphoma</td>
<td>5</td>
</tr>
<tr>
<td>Myelodysplastic syndrome</td>
<td>5</td>
</tr>
<tr>
<td>No identifiable cause</td>
<td>15 to 25</td>
</tr>
</tbody>
</table>


CLINICAL PRESENTATION:

The symptoms and signs of anaemia in elderly are usually insidious. Many elderly patients adjust their activities as their bodies make physiologic adaptations for the conditions. Symptoms relate to the rapidity of the anaemia, the degree of fall in Hb and concomitant medical conditions. The non specific nature of anaemia related symptoms pose a major challenge. Nevertheless, a detailed history often identifies the presence of anaemia related symptoms. Special attention should be paid to elements that indicate a cause for the anaemia and symptoms related to anaemia.

Most symptoms of anaemia are non-specific, however a temporal relation between falling Hb and symptom exacerbation is very useful. History of blood loss should be directly enquired about. General symptoms include – fatigue, weakness, dyspnoea on exertion, tinnitus, palpititation, syncope, headache, poor concentration, pale skin, dark urine, jaundice, dementia, dysphagia. The physical examinations may uncover an anaemic etiology, sign related to anaemia or both. Thus the examination must be comprehensive. Special attention should be paid to – pallor, icterus, lymphadenopathy, tachycardia, cardise murmurs, hepatomegaly, splenomegaly, oedema and stool for colour. Pallor can be the most important diagnostic clue. Conjunctival pallor is a reliable sign, and its presence should prompt the clinician to order blood test for anaemia. In the elderly, anaemia results in a decrease in physical performance and strength as shown by poor balancing walking abilities and hand grip strength. Impairment in cognitive function is also seen in elderly anaemic patience.

EVALUATION:

Anaemia in the elderly is evaluated in a manner similar to that in younger adults, including an assessment for hemolysis, nutritional deficiencies, gastrointestinal bleeding, chronic infections, malignancy, hepatic or renal disease and other chronic diseases. In most elderly patients with anaemia, red cell indices disclose normocytic normochromic anaemia. It also should be remembered that the cause of anaemia is not always found in some cases. In patients without evidence of an underling diseases, the initial laboratory examination should include a full blood picture, red blood cell indices, a reticulocyte count and peripheral blood smear. The laboratory test would include hepatic and renal function, serum ferritin and serum B12 level and stool for occult blood. GI endoscopy is useful in patients with documented Iron deficiency anaemia i.e. low serum ferritin, and not as a routine screen for elderly anaemic patients. Bone marrow examination is indicated in patients with suspected marrow pathologies such as myelodysplastic syndrome (MDS)/ acute myeloid leukemia (AML), multiple myeloma or secondary deposit from malignancy elsewhere.

PHYSIOLOGICAL ADAPTATIONS IN ANAEMIA

Tissue hypoxia develops when compensatory physiological adjustments that enhance release of oxygen from haemoglobin, and increased the flow of blood to the tissues, fail to counteract the affect of the decreased oxygen carrying capacity of the blood caused by the subnormal level of haemoglobin. Hypoxia causes impairment of functions in many tissues, and the symptoms and signs of anaemia are therefore referred to many systems. The degree of functional impairment of individual tissues depends largely on their oxygen requirements, and thus symptoms referable to systems with high requirements, such as the skeletal musculature during activity, the heart and the central nervous system, are particularly prominent.

Several mechanisms are brought into play in anaemia to make more effective use of the available haemoglobin for delivery of oxygen to the tissue. A greater proportion of oxygen attached to haemoglobin is released when the red cell passes through the tissues in anaemic subjects. This results from the increase in concentration of 2,3- diphosphoglycerate which takes place in the red cell in anaemia, the oxygen dissociation curve is shifted to the right, and a greater proportion of the oxygen on the haemoglobin molecule is released at the partial pressure of oxygen of venous blood. It has been calculated that the extent of changes in the oxygen dissociation curve that occurs at a haemoglobin level of 5g/dl is accompanied by release of a further 90% of the oxygen attached to the haemoglobin of the red cell. The volume of the blood is maintained within approximately normal limits by an
increase in the volume of the plasma to counteract the decrease in the volume of red cells. A relatively rapid flow of fluid from the extravascular to the intravascular space occurs after acute blood loss, and along with other changes, results in restoration of the circulatory volume after 48 to 72 hours. Adjustment occurs insidiously in more slowly developing forms of anaemia. Some deviation of blood flow occurs from tissues with lesser oxygen requirements to those with greater requirements. Thus, skin blood flow is reduced, while cerebral and muscle blood flow are increased. Cardiac output increases in anaemia, mainly as a consequence of increased stroke volume. This high output state increases oxygen delivery to tissues by increasing the flow of blood through them, and tends to occur to a progressively increasing extent in resting, otherwise fit individuals as the level of haemoglobin falls below 7g/dl.

PATHOPHYSIOLOGY:

Haematopoiesis, the production of blood elements occurs in

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Flow chart showing evaluation of anaemia

Anemia documented: hemoglobin < 12 g per dL (120 g per L) in women and < 13 g per dL in men (130 g per L)

Perform physical examination looking for signs of renal or hepatic failure evaluate for gastrointestinal or genitourinary blood loss

Check CBC including indices, reticulocyte count and peripheral smear; calculate reticulocyte index

Peripheral smear suggests cause; pursue etiology appropriately

Reticulocyte index < 2: inadequate response

Reticulocyte index ≥ 2: adequate response; suspect blood loss or red cell destruction

RBC indices

MCV ≥ 100 µm³ per cell (80 fL)

Consider alcoholism, hypothyroidism and hepatic disease

Check vitamin B₁₂ and folate levels

B₁₂ deficiency

Check MMA and homocysteine levels.

MMA elevated

Obtain iron studies and ferritin level if not already done; if results are normal, anaemia is of unknown cause.

Consider bone marrow biopsy

Transfusion or trial of erythropoietin if anaemia is clinically significant

Treat with oral B₁₂ 1,000 to 2,000 µg daily

MCV < 100 µm³ per cell (80 fL)

Consider renal disease.

Check serum iron, TIBC, iron saturation and ferritin the most reliable abnormality is a low serum ferritin level

Folate low

MMA and homocysteine normal

Homocysteine elevated, MMA normal

Folate deficiency

Iron < 60 µg per dL (11 µmol per L) TIBC < 250 µg per dL (45 µmol per L) Saturation < 20% Ferritin > 100 ng per mL (100 µg per L)

Iron ≥ 60 µg per dL TIBC ≥ 250 to 400 µg per dL (45 to 72 µmol per L) Saturation ≥ 20% Ferritin 15 to 100 ng per mL (15 to 100 µg per L)

Iron ≥ 60 µg per dL TIBC > 400 µg per dL Saturation < 16% Ferritin < 15 ng per mL

Anemia of chronic disease

Suspect iron deficiency, but evaluate for B₁₂ and folate deficiency if this has not been done; if results are normal, treat as iron deficiency.

Consider treatment with erythropoietin, 50 to 100 U per kg three times weekly

Treat with folic acid, 1 mg daily.

Consider bone marrow biopsy if no response to iron therapy.

Treat with feroxous sulfate, 325 mg daily

Recheck reticulocyte count in 1 to 2 weeks after treatment is started

adopted from Douglas L Smith – anaemia in elderly
an elderly, hierarchical fashion. Blood cell production requires stem cell, a functioning bone marrow microenvironment, nutrients and cytokines. A pluripotent hematopoietic stem cell gives rise to committed progenitors of myeloid, erythroid, and megakaryocytic lineages. Erythropoiesis specifically relates to the arm of haematopoiesis that generates erythrocytes. The earliest committed erythroid lineage progenitors include the BFU-E (burst-forming unit-erythroid) which letter give rise to CFU-E (colony-forming unit erythroid). Normal erythropoiesis in adults occurs exclusively in the bone marrow and is generally restricted to the pelvis, vertebral, sternum, ribs and proximal femurs.

Various haematologic growth factors support stem cell proliferation, differentiation and survival. Erythropoietin (EPO) a glycoprotein, haematopoietic growth factor; severe as a primary regulation of RBC production15. Synthesis and EPO regulation occurs primarily in the kidney with smaller contribution by liver hepatocytes15. As a consequence of renal failure inexorably leads to anaemia from impaired EPO production.

The discovery of hepcidin has considerably clarified the pathophysiology of anaemia of chronic inflammation. Hepcidin is a hepatically synthesized 25 amino acid peptide that severs as a primary regulator of iron homeostasis. Hepcidin directly inhibits ferroprotein, a protein that transports iron out of cell that store it. Inflammation particularly with IL-6, increases hepcidin expression16.

Reduced tissue oxygenation, typically from anaemia or hypoxia, potentially stimulates a logarithmic enhancement of EPO synthesis. Elevated serum EPO level enhance erythrocyte production primarily by inhibiting apoptosis of erythroid progenitor cells and to a lesser degree by enhancing erythroid progenitor proliferation and differentiation17. The reticulocyte, an early RBC that has lost the nucleus but retained the polyribosomal reticular network; eventually emerges into the blood. After 1-4 days, reticulocytes lose this ribosomal network and mature into RBCs. Mature RBCs have an average life span in the blood of 100-120 days. Macrophages engulf senescent RBC, in the spleen, liver and marrow. RBCs are eventually engulfed in the spleen, liver and marrow. RBCs are engulfed in the spleen, liver and marrow. The reticulocyte, an early RBC that has lost the nucleus but retained the polyribosomal reticular network; eventually emerges into the blood. After 1-4 days, reticulocytes lose this ribosomal network and mature into RBCs. Mature RBCs have an average life span in the blood of 100-120 days. Macrophages engulf senescent RBC, in the spleen, liver and marrow. RBCs are eventually engulfed in the spleen, liver and marrow.

IRON DEFICIENCY ANAEMIA:

It has been estimated that 20% of the world population is iron deficient, and the second most common cause of anaemia in the elderly12. Identifying iron deficiency anaemia in elderly persons is essential and be corrected. More importantly, iron – deficiency, particularly in elderly person often points out to an underlying gastrointestinal pathology, including malignancy, NSID induced gastritis, diverticula or angiodysplasia. Older persons may become iron deficient because of inadequate intake or inadequate absorption of iron. Without blood loss, anaemia takes several years to develop. Chronic blood loss from GI malignancy, chronic haemoptysis and bleeding disorders may result in iron deficiency but are much less common cause.

In 20 - 40% of patients the source is in the upper GI tract from peptic ulcer, gastritis oesophagitis or malignancy14. Blood loss from the colon is seen in 15 - 30% of cases, most often causes by colonic malignancy, angiodysplasia, polyps or colitis25. 1 - 15% of patients have blood loss from disorders in the upper and lower GI tract20. The source of blood loss is not found in the 10 - 40% of elderly patients with gastrointestinal symptoms19,20. Patients in whom the gastrointestinal causes is not identified, indicates that most often the anaemia resolves or remains stable with iron replacement20.

The serum ferritin level is the most effective way to diagnosis iron deficiency anaemia. When the serum ferritin is less then 16 ng per ml, iron deficiency is virtually certain15. Iron deficiency is unlikely if the serum ferritin level is greater than 100 ng per ml14. Although ferritin levels between 15 and 100 ng per ml are moderately predictive of iron deficiency anaemia, patients with level in this range may have iron deficiency anaemia, anaemia of chronic disease or both15.

VITAMIN B₁₂ AND FOLATE DEFICIENCY:

Vitamin B₁₂ and Folic acid deficiency are less common and often occur in combination with iron deficiency. Low level of B₁₂ occur in 10 - 15% of the elderly, but it is estimated that only 1 - 2% of the elderly are anaemic due to vitamin B₁₂ deficiency15. Anaemia due to folic acid deficiency are also relatively uncommon in elderly patients15.

Vitamin B₁₂ deficiency rarely is the cause of inadequate intake, except in persons who are strict vegetarian. A common cause is reduced intestinal absorption of vitamin B₁₂. Pernicious anaemia is a classic example of a disorder that causes reduced intestinal absorption of vitamin B₁₂. One study revealed that undiagnosed pernicious anaemia was present in nearly 2% of otherwise healthy individual of 60 years or older15. It also may occur in patients with small bowel disorders and bacterial over growth.

Vitamin B₁₂ deficiency is usually macrocytic and megaloblastic, it is a classic example of a disorder that causes reduced intestinal absorption of vitamin B₁₂. One study revealed that undiagnosed pernicious anaemia was present in nearly 2% of otherwise healthy individual of 60 years or older15. It also may occur in patients with small bowel disorders and bacterial over growth.

Vitamin B₁₂ deficiency is difficult to detect in the elderly. First the symptoms and sign of vitamin B₁₂ deficiency are not reliably present in the elderly. Only about 60% of patients with vitamin B₁₂ deficiency are anaemic37. Second, although anaemia due to vitamin B₁₂ deficiency is usually macrocytic and megaloblastic, it can be normocytic or even microcytic. Third, serum B₁₂ levels do not reliably reflect tissue B₁₂ deficiency. Upto 30% of patients with low normal serum vitamin B₁₂ levels have anaemia and neurologic disease38.

Folate deficiency usually develops as a result of inadequate dietary intake. The body stores very little folate, only enough to last 4-6 months. Like vitamin B₁₂ deficiency, folate deficiency causes macrocytic anaemia, although 25% of elderly patients with folate deficiency have normocytic anaemia1. The symptoms of folate deficiency are nearly undistinguishable from those of vitamin B₁₂.
deficiency.

Studies have shown that the serum methylmalonic acid and homocysteine levels are sensitive for detecting sub-clinical vitamin B12 deficiency, virtually excluding vitamin B12 deficiency when they are normal[9]. These test have become more widely available in recent years, but remain expensive. Similarly between folic deficiency and vitamin B12 deficiency is that the serum folic level can be misleading. The red cell folate concentration is more reliable than the serum level and should be considered. The serum homocysteine level is elevated in 90% of patients with folate deficiency[10], and can be useful for detecting folate deficiency in patients with low normal serum folic levels. If the methylmalonic acid level is also elevated, vitamin B12 deficiency must be considered[11]. Identification of vitamin B12 deficiency is important, because anaemia secondary to vitamin B12 deficiency improves with folate therapy, but folate therapy does not reverse the neurologic damage cause by vitamin B12 deficiency.

ANAEMIA OF CHRONIC DISEASE:

The anaemia of chronic disease (ACD) is common cause of geriatric anaemia, accounting for more than one third of causes[4]. There are three mechanisms involved in the development of ACD – 1) failure of erythropoiesis, 2) lack of iron for haemoglobin synthesis and 3) decreased RBC survival. ACD appears to be primarily related to inflammation, and usually develops in the presence of disorders such as chronic infections, malignancy, autoimmune and inflammatory disorders. Inflammatory markers implicated in anaemia of chronic inflammation include tumour necrosis factor alpha, IL-1, IFN- gamma and IL-6. Recently it has been suggested that hapcidin may be the key mediators in ACD. Hapcidin is key regulator of iron balance, and abnormalities in hapcidin gene expression are associated with clinical abnormalities in iron parameters and anaemia. Hapcidin is an acute phase reactant, and inflammation especially with IL-6, increased hapcidin expression[12].

The haematologic abnormality in anaemia of chronic disease is an impaired ability to use the iron stored in the reticuloendothelial system. The reason the reticuloendothelial cells do not release iron is not known, but experts speculate that, similar to fever, this response aids the bodies defense mechanism[13]. Iron that is held in the reticuloendothelial system is not available for bacterial growth. Nor is the iron available for erythropoiesis, which is the similarity between anaemia of chronic disease and iron deficiency anaemia. The deference, whoever is that the iron stores are normal or between anaemia of chronic disease and iron deficiency anaemia. Nor is the iron available for erythropoiesis, which is the similarity between iron deficiency anaemia and the reticuloendothelial system is not available for bacterial growth.

UNEXPLAINED ANAEMIA:

Multiple studies of anaemia in elderly persons over the past 30 years have confirmed that unexplained anaemia represents a considerable proportion of cases of anaemia in elderly persons[14]. Unexplained anaemia is generally a condition of elderly persons. It appears more commonly with advancing age and is rarely, if ever, encountered in young adults[15]. The cause of the anaemia is not determined in as many as one third of geriatric anaemias. Whether unexplained anaemia represents a spectrum of undiagnosed etiologies or has a unifying pathogenesis remains unclear. Several theories have been postulated to explain this phenomenon, including decreased production of haematologic growth factors, the presence of inflammatory cytokine, marrow abnormalities and androgen deficiencies[16].

MYELODYS PLASTIC SYNDROME (MDS):

MDS occurs in upto 5% of elderly anaemias. It is a clonal marrow disorder characterised by ineffective synthesis of the blood cells[17]. Anaemia is a prominent feature of the disorder. It generally runs a downhill course, though the benign sub-type of MDS patients can have stable disease and can enjoy a long period of good quality life. MDS manifest as irreversible quantitative and qualitative defects of haematopoietic cell caused by abnormal division, maturation and production of erythrocytes, granulocytes, monocytes and platelets. The disorder presents with macrocytosis or a dimorphic red cell morphologic pattern[18]. The median age at which MDS is diagnosed is between 60-75 years. Signs and symptoms are non specific and generally relate to blood cytopenias. Weakness, fatigue and malaise are common. Hepatomegaly is rare, a small percentage of patients have splenomegaly. The most important findings in the bone marrow are the dysplastic changes. The common chromosomal abnormalities seen in MDS are trisomy, loss of the long arm of chromosome 5, 7, 8, or 9 monosomy. The etiology is unknown.

RENAI INSUFFICIENCY:

Chronic kidney disease is an important cause of anaemia in elderly persons, specially considering that renal function declines after aging[19]. Reduced renal EPO production is the primary factor leading to anaemia in chronic kidney disease. Serum EPO levels have been shown to be inappropriately low at a creatinine clearance of less than 40 ml/min. The precise degree of renal dysfunction sufficient to cause anaemia remain controversial. A study among community – dwelling elderly persons suggested anaemia an low EPO levels are independent of age and other factors of a creatinine clearance less than 30 ml/min[20].

THYROID DISEASES:

Hypothyroidism reduces RBC mass and may lead to normocytic anaemia. Occasionally, hypothyroidism may lead to macrocytosis without anaemia[21]. Hypothyroidism and hyperthyroidism may be associated with pernicious anaemia, and both conditions may also lead to a correctable anaemia[22], but most patients with thyroid abnormalities are not anaemic. The degree of thyroid dysfunction leading to anaemia remains unknown. Generally, the more severe the thyroid dysfunction, the more likely anaemia will occur[23].

TREATMENT:

There are no specific clinical guidelines to manage geriatric anaemia at present. It is clear that anaemia in the elderly should be evaluated, and the underling cause should be identified and
treated whenever possible.

Iron deficiency anaemia should be treated with the initiation of iron supplementation. The usual recommended dose of elemental iron is 50–100 mg. three times a day, however a smaller amount of elemental iron such a single dose of iron sulfate, may minimize side effect and improve compliance. Intravenous iron supplementation can be helpful in patients with iron deficiency that failed to respond to oral replacement.

Vitamin B<sub>12</sub> deficiency is treated by vitamin B<sub>12</sub> supplementation. The intramuscular dose is one thousand microgram, often given daily for one week to build up stores, then weekly for one month and monthly thereafter. Oral therapy with 1000-2000 microgram of vitamin B12 daily has been shown to be effective in some way may be superior. Folate deficiency is treated with oral folic acid 1 mg. daily.

There is no specific therapy for anaemia of chronic disease except to treat the underling disorder. Erythropoietin may be helpful. There is no specific therapy for anaemia of chronic disease except to treat the underlying disorder. Erythropoietin may be helpful.

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Treatement of myelodysplastic syndrome for the elderly is mainly supportive – i.e. blood – product support, iron chelating agents for patients who are chronic red cell transfusion dependent and antibiotics for inter-current infections. Newer treatment agents including thalidomide, lenalidomide, hypomethylating agents such as azacitidine have shown good result in MDS.

REFERENCES: