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Infection induced Anemia: A mini Review

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Anemia is reported to be prevalent in approximately 25 % of global population. Approximately 50% of hospitalized patients and 75 % of elderly hospitalized patients are reported to suffer from anemia. Infection induced anemia is the development of anemia due to an infection that could be acute or chronic. Definition of anemia is a hemoglobin level of <13.5g/dl for males and <12.0g/dl for females or a hematocrit level of <41.0% in males and <36.0% in females. When anemia exists in acute and chronic infections, it is due to several factors. Anemia is commonly found in patients with infection and it indicates the disease duration and / or severity. The host produces cytokines in response to infection induced anemia by many well-defined pathophysiological mechanisms. In 18-95% of patients with infection, anemia is present, the prevalence of which is linked to disease severity. Infections caused by bacteria, virus, parasites and fungus can all be accompanied by anemia of inflammation. Anemia is also an important problem in HIV positive individuals in whom it can lead to serious consequences.

Keywords: Infection, Inflammation, Anemia

INTRODUCTION

Anemia

Any of the three clinical conditions must be present to define a patient suffering from anemia; (a) decreased amount of circulating red blood cells (RBCs), (b) decreased amount of hemoglobin (Hgb), or (c) reduction in volume of packed RBCs (Vieth and Lane, 2017). According to The World Health Organization, anemia is defined a hemoglobin level less than 12 g/dL in women and 13 g/dL in men (Cappellini and Motta, 2015).

Types of anemia

Acute anemia

A sudden decrease in the red blood cells, typically brought on by an acute hemorrhage or hemolysis, is referred to as acute anemia (Vieth and Lane, 2017). Since the body doesn't have enough time to adjust and replenish the lost volume, hemoglobin levels of 7 to 8 g/dL are often symptomatic when the decline is abrupt. Due to critical role played by vasospasm and realignment of blood flow, there may be a 20% reduction in blood volume without any noticeable symptom (Demiselle et al. 2020). With increase in loss, patients develop the clinical features of hypovolemia. When compensatory mechanisms such as redistribution of blood flow are no longer sufficient to maintain blood pressure, clinical signs start to show up such as altered mental status, postural hypotension, cool and clammy skin, hyperventilation and tachycardia. Due to the simultaneous loss of red cells and plasma after acute bleeding, hematocrit and hemoglobin levels may be normal; however, this is only visible after the patient's plasma volume has been restored, either naturally or with intravenous fluids. The main therapy used to replace the blood lost in acute anemia is packed red blood cells (pRBCs). The hematocrit is anticipated to rise by 3 points for each unit of pRBCs. Other blood components including cryoprecipitate, fresh frozen plasma (FFP) and platelets are also available for therapy (Napolitano, 2017).

Chronic anemia

Chronic anemia is the type of anemia that arises from chronic diseases. This is a result of long-term health conditions that affect the normal body's function to make red blood cells, such as lupus, Hodgkin's disease, non-Hodgkin lymphoma, breast cancer, autoimmune disorders and rheumatoid arthritis (Schoettler and Nathan, 2018).

Aplastic anemia

Aplastic anemia is an infrequent yet very dangerous blood condition that causes the body to be more prone to infection and bleeding. It is due to reduced amount of blood cell synthesis from the diseased bone marrow. It can be inherited and can be developed at any age. Symptoms of aplastic anemia include easy bruising, fatigue and shortness of breath (Schoettler and Nathan, 2018). Commonly, the cause of damaged bone marrow is from the autoimmune mechanism of destruction of the

stem cells in the bone marrow and as a result, the bone marrow is either empty (aplastic) or contains few blood cells (hypoplastic). Other causes include chemicals from the environment, toxins and chemotherapy. Toxic chemicals, such as pesticides, insecticides, benzene and gasoline have all been linked to aplastic anemia. Viral infections that affect bone marrow such as hepatitis, Epstein-Barr, cytomegalovirus, parvovirus B19 and HIV have also been linked to aplastic anemia (Pascutti, et al. 2016). However, the most common cause of aplastic anemia is autoimmune in which the immune system attacks the stem cells in the bone marrow (Samarasinghe et al. 2018).

Aplastic anemia can be treated by modulating the immune system from destroying the stem cells in the bone marrow and to help the body make new blood cells. Bone marrow transplant which is known as blood and stem cell transplant, may cure aplastic anemia in some people. Most people with aplastic anemia will need a blood transfusion at some point. Aplastic anemia can increase the risk of bleeding, leukemia and other blood disorders. If not treated, aplastic anemia can cause conditions such as heart failure and irregular heart heartbeat **(**Yoshida and Kojima. 2018).

Iron deficiency anemia (IDA)

This type of anemia occurs when there is an imbalance of iron storage, iron intake and loss of iron; this results in insufficient production of erythrocytes. Iron deficiency anemia affects around 30 to 50% of children and other age groups worldwide. Around 1.6 million people are anemic of whom several hundred million manifest iron deficiency anemia (IDA). The most common cause of anemia worldwide is Iron deficiency anemia, it afflicts a subset of two billion people worldwide with nutritional iron deficiency. This has a significant health burden that can be judged from the global prevalence (Pascutti et al. 2013).

Causes

The commonest cause of IDA is blood loss that can be due to bleeding in the gastrointestinal (GI) tract, traumatic injuries, surgeries, menorrhagia, postpartum bleeding and regular use of NSAIDS and aspirin leads to peptic ulcer formation which then causes GI tract bleeding (Drini, 2017). Many infections can cause anemia too (Viana, 2011). Some other causes include abnormalities in iron absorption as in inflammatory bowl disease, ulcerative colitis, Crohn's disease, infection with *Helicobacter pylori*, gastric or intestinal surgeries including bariatric surgery and celiac disease (Nielsen et al. 2015; Bjørklund et al. 2021; Nasif et al. 2021). Medical cause of anemia includes chronic kidney disease as it reduces the production of erythropoietin which is required to make red blood cells. Certain long-term chronic conditions that cause inflammation such as obesity and congestive heart failure affects the ability of the body to regulate and use iron (Portolés et al. 2021). Anemia due to iron deficiency significantly reduces the levels of iron and ferritin (Table-1).

Diagnosis

Diagnosis is made by Complete blood count, Hb levels and the level of ferritin.

Table 1: Iron and ferritin levels in normal individuals and patients with iron deficiency anemia.

Iron, umol/L	**Normal**	**10-30**
	Iron deficiency anemia	Less than 10
Ferritin, ug/L	Normal	Men 40 to 300 Women 20 to 200
	Iron deficiency anemia	Less than 10

Symptoms of IDA

Patients diagnosed with mild to moderate anemia are asymptomatic. More serious IDA causes symptoms of anemia such as breathlessness, fatigue, tiredness, chest pain, dizziness, lightheadedness and cold hands and feet (Kumar et al. 2022).

Treatment

- ➔ Iron supplements: Iron supplements increase the content of iron in the body and is the most prescribed treatment for IDA. It can take anywhere from 3-6 months to restore the level of iron in the body. Side effects of this therapy includes vomiting, nausea, constipation and dark colored stools.
- ➔ IV iron: This is used in more severe cases of IDA and in patients who are non-compliant to oral treatment.
- ➔ Medicines: These include ESA (Erythropoiesis stimulating agent) that increases the RBC production by the bone marrow. These are usually prescribed to Chronic kidney disease (CKD) patients with iron deficiency anemia.
- ➔ Blood transfusions: This is the fastest method of increasing the amount of red blood cells and is usually used to treat severe IDA not responding to other treatment options or in emergency situations (Jimenez et al. 2015).

Pernicious anemia

This type of anemia results from Vitamin B12 deficiency due to reduced levels of intrinsic factor that binds to cobalamin in the terminal ileum. This is an autoimmune condition with the presence of gastric autoantibodies against both intrinsic factor and parietal cells. Pernicious anemia correlates with genetic and autoimmune diseases. It is insidious in onset and can present with pallor, fatigue, paresthesia, incontinence,

generalized weakness and psychosis. Treatment aims at increasing the levels of Vitamin B12 by intramuscular injections or oral supplementation. Pernicious anemia can be fatal and lead to neurologic sequelae if it remains undiagnosed and untreated for long periods of time (Tran and Tran. 2018). Pernicious anemia can also present with pseudo thrombotic microangiopathy which is due to the cytoskeletal fragility of RBC that contributes to schistocyte formation depending on the severity of dyserythropoiesis. Clues leading to the diagnosis of pernicious anemia on peripheral blood smear include the presence of macroovalocytes (Veit, 2017).

Treatment of cobalamin deficiency

Cobalamin replacement corrects the reduced hemoglobin levels and the neurological complications can only be reversed if the treatment is initiated early on. Therapeutic recommendations, dosage and administration of vitamin B12 are conflicting. In the USA, those with pernicious anemia are administered cobalamin injections of 1mg/d in their first week of treatment and in the following months they receive an injection every week followed by one every month (Carmel, 2008). On the other hand, patients in Denmark receive 1 mg/week injection of cyanocobalamin during the first month of treatment; this is followed by 1mg injections once every 3 months or 1 mg hydroxocobalamin every alternate month. Higher doses of cobalamin are used to prevent relapse in this situation. Patients are administered injections of 5mg/d cyanocobalamin for 5 days which refill the body's vitamin B12 stores. Following this, B12 stores are kept within the therapeutic range by administering intramuscular injection of 5 mg cyanocobalamin once in 3 months. Patients are monitored at least once in a year by performing basic investigations like serum cobalamin, ferritin levels and a complete blood count (Devalia et al. 2014).

Hemolytic anemia

Hemolytic anemia is described as anemia brought on by the early destruction of RBC, which results in a shorter RBC survival time. Hemolytic anemia can be brought on by a wide range of diseases, from moderate to potentially fatal, hereditary and acquired, acute and chronic (Dhaliwal et al. 2014). Hemolytic anemias have similar systemic symptoms like anemias, such as pallor, fatigue, dizziness, and weakness. Jaundice and / or scleral icterus may develop, and the spleen may enlarge. Patients with anemia and reticulocytosis might have hemolysis. A peripheral smear is examined, and blood levels of bilirubin, LDH, haptoglobin, and ALT are evaluated if hemolysis is suspected. The most crucial tests to identify hemolysis are peripheral smear and reticulocyte count. The cause of hemolysis can be determined using antiglobulin testing or hemoglobinopathy screening using, for example, high-performance liquid chromatography (HPLC) (Brodsky, 2019). Transfusions, plasma exchange, hydration, and hemodynamic support are a few of the interventions that may be necessary before the cause of hemolysis is identified. The specific treatment required depends on the mechanism causing the hemolysis (Dhaliwal et al. 2004).

Mammalian iron metabolism

Iron is important for all organisms mainly due to its capability to donate and accept electrons. Iron acts as a cofactor for many proteins and enzymes for the metabolism of oxygen and energy. Disruption of iron homeostasis may be induced by different human diseases including iron deficiency anemia, leading to oxidative damage (Pantopoulos et al. 2012). The hormone hepcidin and iron regulatory proteins have been shown to secure iron balance. Iron metabolism is stabilized by regulatory systems. It relies on the hormone hepcidin and the iron exporter ferroportin, controlling cellular iron metabolism through iron regulatory proteins (Rauner et al. 2019).

Around 1–3 mg of iron is absorbed by humans every day, to compensate for losses of iron through urine and sweat. Mammals do not have a modulated physiological mechanism for iron excretion and intestinal iron absorption is an adjusted process. Enterocytes absorb the dietary non-heme ferric iron by divalent metal transporter 1 (DMT1), reduced by membrane bound ferric reductases and duodenal cytochrome b (CYBRD1/DCYTB) (Gulec et al. 2014). Enterocytes also consume heme iron. Cellular iron is changed through enterocyte and is transported into the circulation by the basolateral exporter ferroportin (Knutson, 2017).

Diferric Tf (Tf-Fe(III) is the most important form of iron for cells with erythroid precursors present, as iron is essential for heme synthesis. Iron export relies on iron oxidation through the membrane bound multicopper oxidase hephaestin allowing it to bind to plasma transferrin (Tf) (Kafina and Paw, 2017). Tf-Fe(III) binds to cell surface transferrin receptor-1 (TFRC). Then internalization of the Tf-Fe(III)-TfR1 complex is mediated by clathrin mediated endocytosis. Ferric iron is released from Tf and reduced by STEAP3, which is then transported into the cytosol by DMT1. Systolic iron is used for the arrangement of mitochondria for biosynthesis of Fe-S clusters and heme also for iron containing proteins. When the body has adequate amounts of erythropoiesis and iron stores, iron from enterocytes is decreased by hepcidin mediated internalization and degeneration of ferroportin. As a result, iron is stored in ferritin. Iron lasts for 3 days in ferritin after that it undergoes desquamation of intestinal cells (Waldvogel-Abramowski et al. 2014).

HIV and Anemia

Anemia in HIV positive individuals has serious complications affecting the quality of life and function and in most severe cases reducing the life expectancy (Melese et al. 2017). In Ethiopia, where both HIV and undernutrition are high, the presence of anemia in HIV patients had a negative effect on the progression of HIV

and the quality of life. Anemia is an important problem in these patients, some of the causes include blood loss that can be associated with neoplastic conditions like lesions due to Cytomegalovirus and Kaposi sarcoma. Pathophysiology of HIV includes: increased RBC destruction, decreased RBC synthesis and ineffective RBC production (Beyene et al. 2017).

Reduced Red blood cell production: Infiltration of the bone marrow by cancer, infection or myelosuppression like chemotherapy significantly reduces RBC production. Table 2 shows the anti-infective agents which are reported to have a negative effect on RBC production. HIV infection reduces the synthesis of erythropoietin and leads to a reduced erythropoietin response (Peng et al. 2022).

Table 2: Anti-infective agents with negative effect on RBC production.

Antifungal agents
Antiretrovirals
Zidovudine
Foscarnet
Doxorubicin
Methotrexate
Amphotericin
Vinblastine
Anti-Pneumocystis carinii agents
Sulfonamides
Paclitaxel

Increased hemolysis: Premature or accelerated destruction of the RBC in the spleen and circulatory system can occur in HIV positive individuals. In addition, hemolytic anemia results from autoantibodies, disseminated intravascular coagulation, G6PD deficiency, thrombotic thrombocytopenic purpura and hemophagocytic syndrome (Araujo et al. 2019).

Ineffective RBC production: Anemia can be a consequence of nutritional deficiencies most often that of cobalamin, folic acid or Iron. Folic acid deficiency in HIV infected patients is caused by a diet poor in folate or a pathology in the jejunum. B12 deficiency results from malabsorption in the ileum or due to gastric pathology caused by infections (Santis et al. 2011).

Risk factors for Anemia in HIV patients

Risk factors are listed in Table 2. A retrospective study of prevalence, risk factors and mortality due to anemia in combined antiretroviral treatment-naive HIV-infected patients in China was carried out in 2017. The results of which showed that higher HIV RNA load was independent to increasing the prevalence of anemia which may be due to a higher number of patients with higher HIV RNA loads and different HIV RNA stratified method (Dai et al. 2017).

Table 3: Various risk factors commonly associated with anemia in patients with HIV.

CD4 cell count < 200 cells /dL
History of clinical AIDS
Women
Black race
Increasing age
Zidovudine use
Plasma virus load
Lower BMI
Oral Candidiasis
History of fever
History of bacterial pneumonia

HAART therapy and the prevalence of anemia

Approximate 10% of patients with HIV infection suffer from anemia. The various risk factors associated with anemia in HIV patients are listed in Table 3. HAART has significantly reduced the prevalence of anemia. A total of 1624 patients were part of the EuroSIDA study, before initiating HAART, mild anemia as defined by hemoglobin level of <12g/dl in females and <14 g/dl in males was present in 64% and severe anemia is a hemoglobin level of <8 g/dl for men and women was present in 1.2 %. After 1 year, improvements were recorded with 45.6% of patients illustrating mild anemia and 0.6% with severe anemia. Anemia still remains associated with HIV progression despite the use of HAART (Nissenson et al. 2005).

Mechanism of infection induced anemia

Infection and anemia have an intriguing and complicated interaction. Infection can directly cause anemia by leeching blood-forming elements, destroying circulating red blood cells, lowering bone marrow production, accelerating extravascular hemolysis, or any combination of these. It can also generate anemia indirectly by triggering an antigen-antibody interaction (Viana, 2011)

Correlation exists between the activity of the linked disease and the severity of anemia-induced infection. The development of anemia-induced infections may be influenced by immune and inflammatory response mediators like tumor necrosis factor (TNF), interferons (IFN) and interleukin-1 (IL-1), according to a common pathophysiological mechanism encompassing diseases with autoimmune, microbial, and clonal origins (Hurrell, 2012).

The pathophysiology of infection induced anemia involves three processes: decreased red cell survival, which demands for a minimal increase in red cell production by the bone marrow, but to which the marrow is unable to effectively react due to impaired erythropoietin (EPO) synthesis, impaired erythroid progenitor response to EPO, and decreased mobilization of reticuloendothelial system iron reserves. All of these processes can be

mediated by inflammatory cytokines (Morceau et al. 2009). Figure 1 shows how infection and inflammation can induce anemia.

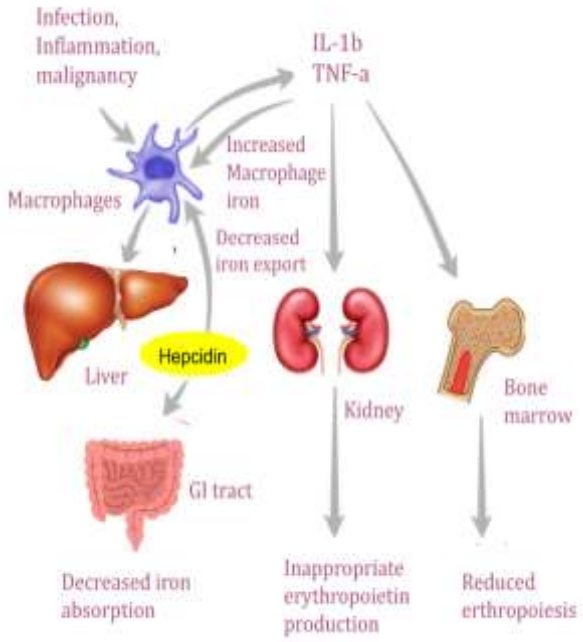

Figure 1: Mechanism of infection and inflammation induced anemia

A potential mechanism infection and inflammation induced anemia involves immune cells and interleukins. The macrophage is prompted to synthesize IL-6 and IL-1b in the presence of infection, inflammation, or malignancy, which triggers the liver to release hepcidin. Hepcidin, in turn, prevents iron absorption from the gastrointestinal tract and reduces iron release from macrophages through its interaction with the iron export protein ferroportin (Nemeth and Ganz, 2009). Both outcomes result in the decreased plasma iron levels (hypoferremia), which are suggestive of an anemia caused by infection. The synthesis of erythropoietin, the lifespan of red blood cells, and the effectiveness of erythropoiesis are all decreased by inflammatory cytokines like IL-1b and TNF-a, which are also elements of infection induced anemia (Vieth and Lane. 2017).

Subclinical Infection and Anemia:

Iron is an immunomodulating nutrient that modulates immune responses in both the humoral and cellular immune systems. This micronutrient is crucial for a healthy immune system because it is involved in wide range of functions. Therefore, during an illness, the need for this mineral rises, worsening the patient's iron status (Napolitano. 2017). Acute phase proteins (APP), such as C-reactive protein (CRP), are known to fluctuate in serum concentration during infectious processes. Indicators of subclinical infection include the CRP plasma levels, which significantly rises within about 10 hours of the beginning of acute inflammation. Additionally, during infectious processes, there is less iron available for the production of hemoglobin due to the retention of intracellular iron, such as ferritin, and decreased blood transport of iron due to lower concentrations of the enzyme that transports ferritin (Knutson, 2017). Thus, modifications to the activities of storage and transport are additional reasons that account for a decrease in iron concentrations during infections. Especially in populations where infection rates are frequently high, the presence of even subclinical illness is a factor that might lead to an overestimation of iron-deficiency anemia (Sales et al. 2011).

Proinflammatory cytokine and anemia :

Cytokines greatly affect the regulation of inflammatory response. Aging which could be the cause of increase of proinflammatory cytokines such as CRP, IL-6, IL-1, TNF alpha) which has been shown to inhibition of erythropoietin and cause anemia (Ershler, 2003) antimicrobial protein levels such as defensin and hepcidin were shown to be elevated. AMPs are important for innate immunity and function in apoptosis and wound healing (Wang. 2014). Hepcidin is a hormone which produced in the liver. It works as an antimicrobial protein as it has antibacterial and antifungal characteristics. It can control the way iron is exported from enterocyte to the plasma in the small intestine. Recent studies have shown that during infection and inflammation, hepcidin synthesis is greatly increased, in direct proportion to the stimulation of IL-6 (Askar et al. 2017).

CONCLUSION

Interplay between human iron status and risk of infection is complex and multifactorial. However, it has been revealed in different studies involving different pathogens that anemia is associated with increased mortality due to infection. Our knowledge on the mechanism of infection induced anemia has increased in past years. However, it is often difficult to differentiate between infection induced anemia and anemia due to iron deficiency and suitable biomarkers are lacking. Detailed mechanisms of cytokine produced following infection and how these molecules modulate iron status in the host is beginning to be explained. Therapeutic efficacy of different established and novel therapeutic procedures is being tested. However, the complex interaction between infection and anemia needs to be elucidated completely so that a universally acceptable guideline can developed for treatment of affected people.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

QSG, MM and MA collected the information and prepared the manuscript. AH reviewed and edited the manuscript. All authors read and approved the final version.

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