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Review Article

Pathophysiology, Prevalence, and Management of Iron Deficiency Anemia

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ABSTRACT

Anemia is a major killer in India. Statistics reveal that every second Indian woman is anemic. One in every five maternal deaths is directly due to anemia. Anemia affects both adults and children of both sexes, although pregnant women and adolescent girls are most susceptible and most affected by this disease. Iron deficiency is the most common micronutrient deficiency which affects more than 2 billion population worldwide, leading to anemia in more than 40% of women of reproductive age developed countries. The prevalence of anemia among adolescent is more than 25% in developing countries. Globally, anemia affects 1.6 billion people which correspond to 24.8% of the population. The highest prevalence is in the preschool age children 47.4%, prevalence in men is 12.7% the groups with higher prevalence are, infants and children of 1–2 years 48%, School children are about 40%, non-pregnant women 35%, adolescents 30–55%, and preschool children 25%. The prevalence of anemia in developing countries is about 4 times than those of developed countries. Asia has the highest rates of anemia in the world. About half of the world's anemic women live in Indian sub-continent and 88% of them develop anemia during pregnancy. The situation in Asia has not improved in recent years. Almost all individuals will be iron deficient except possibly if the anemia is caused predominantly by malaria. This review contains detailed information about types and prevalence of anemia, including special emphasis of pathophysiological aspects and treatment management of iron deficiency anemia.

Keywords: Anemia, Ferritin, Folic acid, Iron, Megaloblastic anemia

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Introduction

Anemia – an ailment in which hemoglobin (Hb) concentration and/or red blood cell (RBC) numbers are lower than usual and deficient to meet a person's physiological needs affects a third of the world's population and contributes to increased morbidity and mortality, decreased work productivity, and impaired neurological development.[1]

RBCs are highly specialized for their oxygen transport function. Each one contains about 280 million Hb molecules. A Hb molecule consists of a protein called globin and non-protein pigments called hemes. Each heme contains an iron that can combine reversibly with one oxygen molecule. The oxygen is transported to other tissues of the body. In the tissues, the iron-oxygen reaction reverses. The Hb releases oxygen, which diffuses into the interstitial fluid and from there into cells. Normal values for Hb are 14–20 g/100 ml of blood in infants, 12–15 g/100 ml in adult females, and

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14–16.5 g/100ml in adult males. A healthy male has about 5.4 million/mm^3 of RBCs of blood and a healthy female has about 4.8 million. The process of erythrocyte formation is called erythropoiesis.[2]

As per the report of The State of the world's Children, Comilla, Bangladesh, (2011), reveals that adolescent females are more prone to nutritional difficulties than adolescent males. In early childhood (0–4 years), the available international evidence suggests that differences in nutritional status between girls and boys are statistically negligible in all region expect South Asia. Now a days, however, girls run a greater risk than boys of nutritional difficulties, notably anemia. Data from 14 developing countries show a considerably higher incidence of anemia among female adolescents aged 15–19 as compared to their male counterparts in all but one country. In nine countries – all, aside from India, in West and Central Africa – more than half of girls aged 15–19 are anemic. India also has the highest underweight prevalence among adolescent girls among the countries with available data, at 47%. The implications for adolescent girls in this country are particularly serious, given that in the period 2000–2009, around 47% of Indian women aged 20–24 were married by age 18 years. Adolescent pregnancy is a regular consequence of child marriage and underweight mothers have a higher risk of maternal death or morbidity.[3]

Types of Anemia

Anemia is broadly classified depending on its pathophysiological features [Figure 1].

Iron deficiency anemia (IDA)

IDA is the most common anemia occurring in inflammatory bowel disease (IBD), and its prevalence ranges from 36% to 76% patients.[4] The prevalence of mild-to-moderate anemia between 1993 and 2003 has decreased, what may results from a wider availability of immunosuppressive treatment. However, the prevalence of severe anemia remained unchanged. Healthy people supply in a diet approximately 5–15 mg of elemental iron and 1–5 mg of heme iron daily, of which approximately 1–2 mg is absorbed in the intestine, mainly in the duodenum; only some amount of iron is lost with feces.[5] Heme iron, which is supplemented mainly with animal products, for example, myoglobin meat, poultry, and fish, is easily absorbable, and its absorption is not influenced by other dietary components. Conversely, non-heme iron can be found mostly in plant food. Absorption of inorganic iron is low and depends on many dietary constituents. Phytate, oxalate, polyphenols, and tannin, frequently occurring in plants, diminish the uptake of inorganic iron.[6,7] Some drugs, for example, commonly used proton pump inhibitors also weaken the process. Finally, avoidance of ingesting dairy products could facilitate iron supplementation, as calcium inhibits absorption of both iron forms [Figure 2].[8,9]

Megaloblastic anemia

Megaloblastic anemia is a general term used to describe a group of anemia caused by impaired DNA synthesis. It is characterized by abnormal findings in peripheral blood smear (macroovalocytes) and bone marrow samples (megaloblastic hyperplasia). Megaloblasts, the hallmark of these anemia, are caused by asynchronous maturation between the nucleus and the cytoplasm due to DNA synthesis impairment.[10,11] Folic acid and cobalamin are B-group vitamins that play an essential role in many cellular processes. Deficiency in one or both of these vitamins causes megaloblastic anemia, a disease characterized by the presence of megaloblasts. Megaloblasts occur when inhibition of DNA synthesis causes asynchronous maturation between the nucleus and the cytoplasm. Clinical manifestations are similar to those of other types of anemia, with the exception of cobalamin deficiency megaloblastic anemia, which presents distinctive neurological symptoms. An under-standing of the metabolism of these vitamins will enable clinicians to

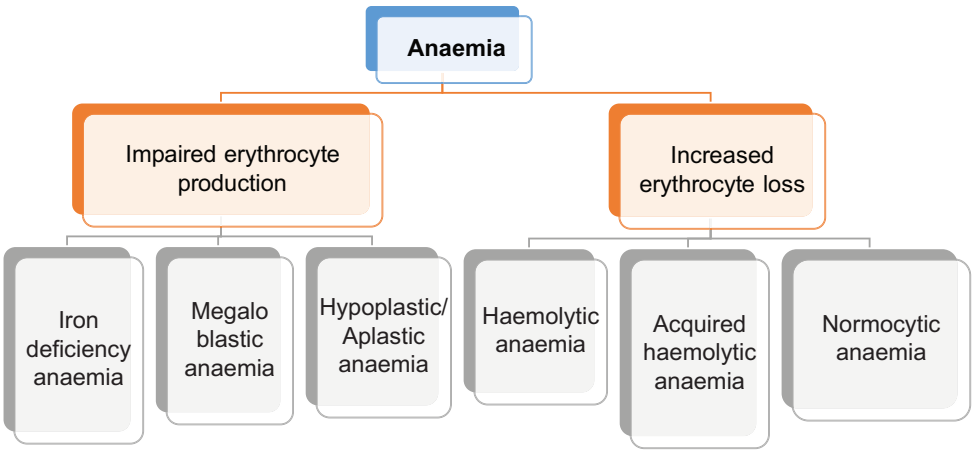

Figure 1: Types of anemia

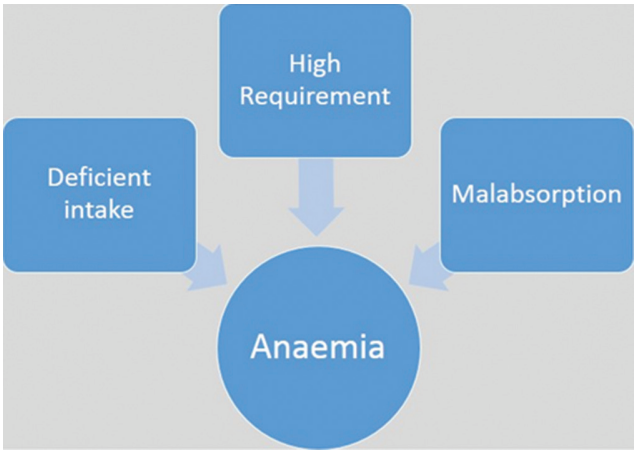

Figure 2: Causes of iron deficiency anemia

make the best use and interpretation of laboratory studies and monitor therapeutic strategies, which consist mainly of administering supplements to restore body reserves.[12]

Hypoplastic/aplastic anemia

Aplastic anemia's long history has produced confusing terminology. "Anemia" derives from early ability to measure RBCs in a hematocrit. Most patients have pancytopenia, with decreased platelets and white blood cells. "Aplastic" refers to the inability marrow to form blood, the end organ effect of diverse pathophysiologic mechanisms. Historically, identification of aplastic anemia was postmortem, and the biopsy remains fundamental to diagnosis. Yet a seemingly empty bone marrow may be entirely capable of supporting normal hematopoiesis. Conversely, bone marrow failure can occur with normally cellular marrow, as in the myelodysplastic syndromes (MDS) and paroxysmal nocturnal hemoglobinuria (PNH). Two interrelated explanations exist for aplastic anemia: Extrinsic immune-mediated suppression of hematopoietic stem cells and intrinsic abnormality of marrow progenitors. Damaged hematopoietic stem cells mature into self-reactive T-helper cells (T1) that release cytokines interferon-? and tumor necrosis factor to propagate a cytotoxic cascade to kill and suppress other hematopoietic stem cells. The exact antigens T1 cells target are unclear, but one appears to be the glucose phosphate inositol-linked protein on cell membranes (the mechanism behind pancytopenia in PNH). Furthermore, the genes for apoptosis and death pathways are upregulated. Moreover, immunosuppressive therapy targeting T-cells leads to a response in two-thirds of patients with idiopathic aplastic anemia, and patients with graft-versus-host disease develop aplasia in the setting of healthy bone marrow progenitors. In the second theory, stem cells with inherent defects lose the capacity to differentiate and proliferative. Their inability to dedifferentiate can lead to clonal evolution into hematologic neoplasms, for example, MDS. This is common in patients with Fanconi anemia. Partial defects in telomeres, the component of DNA intertwined with cell division, lead to premature hematopoietic stem cell exhaustion and marrow aplasia as well. Shortened telomeres are present in cells of half the patients with aplastic anemia.[13]

Hemolytic anemia

Hemolysis is the premature destruction of erythrocytes. A hemolytic anemia will develop if bone marrow activity cannot compensate for the erythrocyte loss. The severity of the anemia depends on whether the onset of hemolysis is gradual or abrupt and on the extent of erythrocyte destruction. Mild hemolysis can be asymptomatic while the anemia in severe hemolysis can be life threatening and cause angina and cardiopulmonary decompensation.[14] Autoimmune hemolytic anemia (AIHA) is caused by the increased destruction of RBCs by anti-RBC autoantibodies with or without complement activation. RBC destruction may occur both by a direct lysis through the sequential activation of the final components of the complement cascade (membrane attack complex), or by antibody-dependent cell-mediated cyto-toxicity (ADCC). The pathogenic role of autoantibodies depends on their class (the most frequent are IgG and IgM), subclass, thermal amplitude (warm and cold forms), as well as affinity and efficiency in activating complement. Several cytokines and cytotoxic mechanisms (CD8+ T and natural killer cells) are further involved in RBC destruction. Moreover, activated macrophages carrying Fc receptors may recognize and phagocyte erythrocytes opsonized by autoantibodies and complement. Direct complement-mediated lysis takes place mainly in the circulations and liver, whereas ADCC, cytotoxicity, and phagocytosis occur preferentially in the spleen and lymphoid organs. The degree of intravascular hemolysis is 10-fold greater than extravascular one. Finally, the efficacy of the erythroblastic compensatory response can greatly influence the clinical picture of AIHA. The interplay and relative burden of all these pathogenic mechanisms give reason for the great clinical heterogeneity of AIHAs, from fully compensated to rapidly evolving fatal cases.[15]

Acquired hemolytic anemia

Acquired hemolytic anemia is among the most frequently reported drug reactions in humans, although it is usually of minor severity. Decreased lifespan of circulating erythrocytes defines hemolytic anemia. This type of anemia can range from subtle erythrocyte membrane changes resulting in premature removal from circulation (extravascular hemolysis) to life-threatening intravascular hemolysis. Hemolytic anemia are often accompanied by a regenerative response manifested by erythroid hyperplasia of the bone marrow and increased circulating reticulocytes.

The peripheral blood smear may show morphologic evidence of erythrocyte destruction, including schistocytes and spherocytes, and occasionally Heinz bodies, and other forms of poikilocytosis depending on the pathogenesis of the anemia. A regenerative response (i.e., reticulocytosis) may not be present if the disease rapidly progresses to death, as is frequently the case with acute intravascular hemolysis. A rapid decline in hematocrit in the absence of overt hemorrhage is compatible with hemolytic anemia. The symptoms of acquired hemolytic anemia relate to the severity of the anemia and the rate of RBC destruction. Anemia may lead to cardiovascular symptoms such as dyspnea, angina, and tachycardia; or nonspecific complaints of generalized malaise and dizziness. Rapid destruction of RBCs can be associated with fever, abdominal pain, back pain, or limb pain, whereas patients with hemolytic anemia that develops gradually are often asymptomatic. Signs of anemia include dyspnea, pallor, jaundice, and brown-discolored urine and in massive acute hemolysis, shock, and renal failure can occur.[16]

Normocytic anemia

Anemia is a common problem that is often discovered on routine laboratory tests. Its prevalence increases with age, reaching 44% in men older than 85 years. Normocytic anemia is the most frequently encountered type of anemia. Anemia of chronic disease, the most common normocytic anemia, is found in 6% of adult patients hospitalized by family physicians. The goals of evaluation and management are to make an accurate and efficient diagnosis, avoid unnecessary testing, correct underlying treatable causes, and ameliorate symptoms when necessary. The evaluation begins with a thorough history and a careful physical examination. Basic diagnostic studies include the RBC distribution width, corrected reticulocyte index, and peripheral blood smear; further testing is guided by the results of these studies. Treatment should be directed at correcting the underlying cause of the anemia. A recent advance in treatment is the use of recombinant human erythropoietin.[17]

Morphological Classification of Anemia

The most clinically useful classification system is based on the mean corpuscular volume (MCV).

- Microcytic (MCV < 80 femtoliters [fL]).
- Normocytic (MCV 80–100 fL); further subclassified according to the reticulocyte count as:

Hyperproliferative (reticulocyte count >2%): The proportion of circulating reticulocytes increases as part of a compensatory response to increased destruction or loss of RBCs. The cause is usually acute blood loss or hemolysis.
Hypoproliferative (reticulocyte count <2%): These are primarily disorders of decreased RBC production, and the proportion of circulating reticulocytes remains unchanged.

- Macrocytic (MCV > 100 fL); further subclassified as:

Megaloblastic: A deficiency of DNA production or maturation resulting in the appearance of large immature RBCs (megaloblasts) and hypersegmented neutrophils in the circulation.
Non-megaloblastic: Encompasses all other causes of macrocytic anemia in which DNA synthesis is normal. Megaloblasts and hypersegmented neutrophils are absent.

Management of IDA

Patients with IDA of uncertain etiology are usually referred to a gastroenterologist because gastrointestinal (GI) conditions are the most common causes[18,19] with only menstrual blood loss in premenopausal women a more frequent cause. This article concurs with most of the recommendations of the British Society of Gastroenterology;[20] however, we propose an alternative, streamlined management algorithm [Figure 3].[21]
There is clear evidence to support prompt treatment in all patients with IDA because it is known that treatment improves quality of life and physical condition as well as alleviates fatigue and cognitive deficits.[22] Although clear evidence is lacking, iron deficiency without anemia is associated with restless legs syndrome (RLS) and chronic fatigue, and treatment alleviates these symptoms.[23] The treatment of IDA in patients with chronic kidney disease, congestive heart failure, or cancer should be undertaken in conjunction with the appropriate specialists because different guidelines may apply.

Oral iron

Intestinal iron absorption is limited. The maximum rate of absorption of 100 mg of oral iron is 20–25% and is reached only in the late stage of iron deficiency. Latent iron deficiency and IDA correspond to mean absorption rates of 10–13%, respectively, whereas healthy males absorb 5% and healthy females 5.6%.[24] Iron that remains in the intestinal lumen may cause mucosal injury and studies in animal models suggest an exacerbation of disease activity and the induction of carcinogenesis in IBD. Furthermore, dose-dependent GI side effects hinder compliance and result in non-adherence in up to 50% of patients.[25] Thus, it is reasonable to adjust the dosage to improve tolerability. Although doses typically range from 100 mg to 200 mg of elemental iron per day, successful repletion can be achieved with doses as low as 15–30 mg of elemental iron daily. Several formulations are available over the counter and are typically composed of ferrous iron salts (e.g., ferrous sulfate, ferrous gluconate, and ferrous fumarate).
Oral iron supplementation is effective when intestinal uptake is intact. However, its use should be limited to patients with

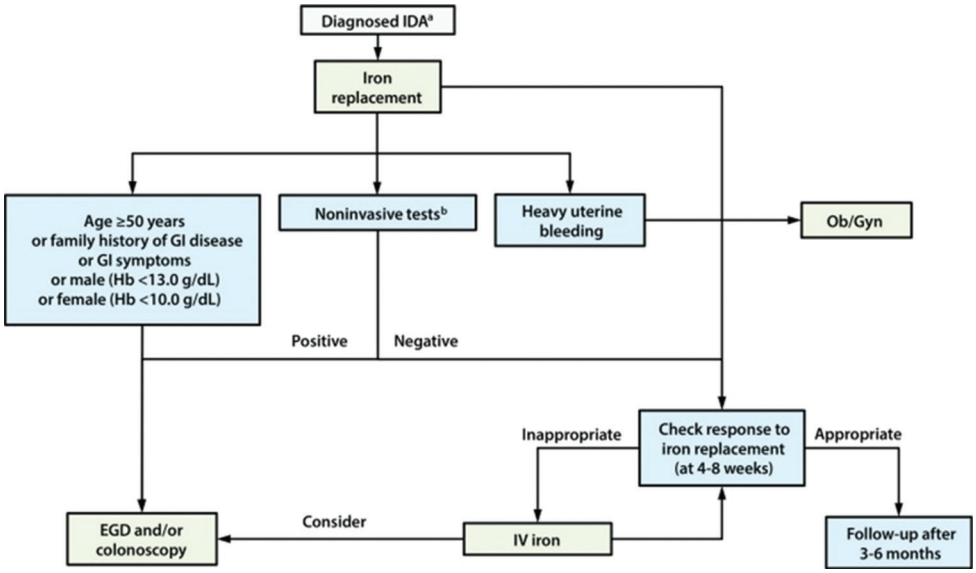

Figure 3: A proposed algorithm for the management of iron deficiency anemia[21]

mild anemia (Hb, 11.0–11.9 g/dL in non-pregnant women and 11.0–12.9 g/dL in men) because repletion occurs slowly. When faster repletion is desired, intravenous administration is the preferred route. Nevertheless, oral iron is readily available, inexpensive, and convenient, making it a viable treatment option.

Conclusion

Anemia is highly prevalent in the general population and in the clinical setting. It is associated with diminished quality of life, worsening of clinical outcome, and increased health-care costs. Iron deficiency is the predominant culprit, and iron deficiency alone may cause fatigue, RLS, and impaired cognitive function. IDA should be treated on diagnosis, and treatment should be considered for iron deficiency without anemia when it is symptomatic. Gastroenterologists have become the central managers of patients with intestinal bleeding or iron malabsorption. They are experts in endoscopic procedures conducted for diagnostic and therapeutic purposes. They should also become experts in iron replacement therapy and be competent in administering iron intravenously when needed.

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