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Outline Review on Anemia

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ABSTRACT

Anemia is one of the most widespread nutritional absence and accounts for almost one half of anemia cases. IDA (Iron deficiency anemia) is a common cause of anemia and is typically due to insufficient intake, poor absorption, or overt or occult blood loss in growing children, adolescents and pregnant women. In most cases, this deficiency disorder may be diagnosed through full blood analysis (complete blood count) and high levels of serum ferritin. However, the underlying cause should be sought in case of all patients. To exclude a source of gastrointestinal bleeding medical procedure like gastroscopy/colonoscopy is utilized to evaluate the level of iron deficiency in patients without a clear physiological explanation. The treatment options include oral iron supplement and intravenous iron therapy. However, this mode of treatment is not tolerable by some patients while it is insufficient in a certain subset of patients. The objective of the review is to provide a critical summary and an update of the diagnosis and treatment options of IDA.

INTRODUCTION:

Malnutrition and poor diets constitute the number-one driver of the global burden of disease[1]. We already know that the annual GDP losses from low weight, poor child growth, and micronutrient deficiencies average 11 percent in Asia and Africa greater than the loss experienced during the 2008–2010 financial crisis. In the United States, for example, when one person in a household is obese, the household faces additional annual health care costs equivalent to 8 percent of its annual income[2]. In China, a diagnosis of diabetes results in an annual 16.3 percent loss of income for those with the disease. All of these figures mean that the burden of malnutrition falls heavily on all of us, whether directly suffering or not. But these costs also represent large opportunities for human and economic betterment, and this report provides many examples of countries that have seized these opportunities to improve the lives of their people and the health of their societies by addressing malnutrition[3].

According to the World Health Organization (WHO), there are two billion people with anemia in the world and half of the anemia is due to iron deficiency**.** Anemia is a decrease in the total amount of red blood cells (RBCs) or hemoglobin in the blood or a lowered ability of the blood to carry oxygen[4]. The three main types of anemia are due to blood loss, decreased red blood cell production, and increased red blood cell breakdown. In women of childbearing age, the most common cause of iron deficiency anemia is a loss of iron in the blood due to heavy menstruation or pregnancy. A poor diet or certain intestinal diseases that affect how the body absorbs iron can also cause iron deficiency anemia. Anemia is a major health problem in India. In the 2005-2006 National Family Health Survey (NFHS-3), a household survey aimed at having national and state representative data on population health and nutrition; the prevalence of anemia was 70% in children aged 6–59 months, 55% in females aged 15–49 years, and 24% in males aged 15–49 years. Although the NFHS-3 showed that the prevalence of anemia was higher in rural areas, there is a paucity of data about the epidemiology of anemia in rural settings. This review describes the prevalence of anemia among patients who attended the outpatient clinics of a rural hospital in Andhra Pradesh, India[5].

MORPHOLOGICAL CLASSIFICATION OF ANEMIA[3]:

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

- Microcytic (MCV typically < 80 μm^3 [80 fL]),
- Normocytic (MCV 80-100 μm^3 [80 to 100 fL]):
- It further subclassified according to the reticulocyte count as:

o 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.

o Hypoproliferative (reticulocyte count<2%):

o These are primarily disorders of decreased RBC production, and the proportion of circulating reticulocytes remains unchanged.

- Macrocytic (MCV>100 μm^3 [100 fL]):
- It further subclassified as:

o Megaloblastic: A deficiency of DNA production or maturation resulting in the appearance of large immature RBCs (megaloblasts) and hypersegmented neutrophils in the circulation.

o Non-megaloblastic: Encompasses all other causes of macrocytic anemia in which DNA synthesis is normal. Megaloblasts and hypersegmented neutrophils are absent.

Table 1: OVERVIEW ON TYPES OF ANEMIA

TYPE OF ANEMIA[6,7,8,9]	**CAUSE**	**SYMPTOMS**	**TREATMENT**	**RISK**
Iron deficiency anemia (IDA)	Iron deficiency occurs when the rate of loss or use of iron is more than its rate of absorption and use	Tiredness, Weakness, shortness of breath, fast heartbeat, glossitis. Angular stomatitis, pica, a craving for strange foods such as starch, ice and clay. Heavy menstrual bleeding or	Dietary changes and supplements, medicines, and surgery. Severe iron-deficiency anemia may require treatment in hospital, blood transfusions, iron rejections or intravenous iron therapy.	Infants and young children, women, and adults who have internal bleeding are at highest risk for iron-deficiency anemia.

		abdominal pain due to peptic ulceration.		
Thalassaemia	Haemoglobin in red blood cells has two kinds of protein chains: alpha globin and beta globin. If your body doesn't make enough of these protein chains, red blood cells don't form properly and can't carry enough oxygen. When these genes are missing or altered, thalassaemias occur.	Pale and listless appearance Poor appetite Dark urine Slowed growth and delayed puberty Jaundice Enlarged spleen, liver and heart Bone problems	People who are carriers or who have alpha or beta thalassemia need little or no treatment. Three standard treatments are used to treat moderate and severe forms of thalassemia; these include blood transfusions, iron chelation therapy, and folic acid supplements.	Family history and ancestry are the two risk factors for thalassaemias.
Aplastic anemia	Damage to the bone marrow's stem cells causes aplastic anemia. In more than half of people who have aplastic anemia, the cause of the disorder is unknown. It toxins, such as pesticides, arsenic, and benzene radiation, chemotherapy, medication of Chloramphenicol, Infectious diseases hepatitis, Epstein-Barr virus, cytomegalovirus, parvovirus B19, and HIV. Autoimmune disorders such as lupus and rheumatoid	Fatigue Shortness of breath Dizziness Headache Coldness in your hands or feet Pale skin, gums and nail beds Chest pains	Blood transfusions, blood and marrow stem cell transplants, and medication. These treatments can prevent or limit complications, relieve symptoms, and improve quality of life. Blood and marrow stem cell transplants may cure the disorder.	People of all ages can get aplastic anemia. However, it is most common in adolescents, young adults and the elderly. Men and women are equally likely to have it.

	arthritis.			
Haemolytic anemia	Early destruction of red blood cells	Jaundice Pain in the upper abdomen Leg ulcers and pain A severe reaction to a blood transfusion	Blood transfusions, medicines, plasmapheresis, surgery, blood and marrow stem cell transplants and lifestyle changes.	Haemolytic anemia can affect people of all ages, races and sexes.
Sickle cell anemia	Sickle cell anemia is an inherited, lifelong disease. People who have the disease inherit two copies of the sickle cell gene – one from each parent.	Fatigue Shortness of breath Dizziness Headache Coldness in the hands and feet Pale skin Chest pain Sudden pain throughout the body is a common symptom of sickle cell anemia. This pain is called a "sickle cell crisis", and often affects the bones, lungs, abdomen, and joints.	Sickle cell anemia has no widely-available cure. However, treatments can help relieve symptoms and treat complications. The goals of treating sickle cell anemia are to relieve pain, prevent infections, eye damage and strokes, and control complications. Bone marrow transplants	Sickle cell anemia is most common in people whose families descended from Africa, South or Central American, Caribbean islands, Mediterranean countries, India and Saudi Arabia.
Pernicious anemia	A lack of intrinsic factor is a common cause of pernicious anemia as the body can't absorb enough vitamin B_{12}. Some pernicious anemia occurs because the body's small intestine can't properly absorb vitamin B_{12} which may be due to the wrong bacteria in the small intestines;	Nerve damage Neurological problems such as confusion, dementia, depression, and memory loss. Symptoms in the digestive tract include nausea and vomiting, heartburn, abdominal bloating and gas, constipation or diarrhea, loss of appetite, and weight loss.	Pernicious anemia is treated by replacing the missing vitamin B_{12} in the body. People who have this disease may need lifelong treatment.	Have a family history of the condition. Have had part or all of your stomach removed. Have certain autoimmune disorders that involve the endocrine glands, such as Addison's disease, type 1 diabetes, Graves' disease, and vitiligo.

	certain diseases that interfere with vitamin B_{12} absorption; certain medicines; surgical removal of part of the small intestine; and tapeworm infection. Sometimes people develop pernicious anemia because they don't get enough vitamin B_{12} in their diets.	An enlarged liver A smooth, beefy red tongue Infants who have vitamin B_{12} deficiency may have poor reflexes or unusual movements, such as face tremors.		Have had part or all of your small intestine removed. Have certain intestinal diseases or disorders that prevent your body from properly absorbing vitamin B_{12}. Take medicines that prevent your body from properly absorbing vitamin B_{12}. Area strict vegetarian who doesn't eat any animal or dairy products and doesn't take a vitamin B_{12} supplement, or if you eat poorly overall.
Fanconi anemia	FA is an inherited disease – it is passed on from parents to children through the genes.	Anemia Bone marrow failure Birth defects Developmental or eating problems	Blood and marrow stem cell transplant Androgen therapy Synthetic growth factors Gene therapy	FA occurs in all racial and ethnic groups and affects men and women equally. You are at an increased risk of developing the disease if you have a family history of FA.

OVERVIEW:

1. IRON DEFICIENCY ANEMIA[6,7,8]:

The most common form of anemia is **iron deficiency anemia** (IDA) which is usually due to chronic blood loss caused by excessive menstruation. Increased demands for iron, such as fetal growth in pregnancy, and children undergoing rapid growth spurts in infancy and adolescence, can also cause iron deficiency anemia.

This condition is treated with iron supplementation as well as the treatment of the underlying cause of the iron deficiency.

Stages of IDA:

Stage I: The first response to negative balance is the increased utilization of iron stores. Tissue iron stores including bone marrow are reduced and serum ferritin levels fall. Hb levels remain within normal limits (WNL).

Stage II: With depletion of iron stores serum iron falls and transferrin levels begin to rise. Hb synthesis decreases with a resultant normochromic, normocytic anemia.

Stage III: With additional reduction in Hb synthesis, hypochromic and microcytic erythrocytes are produced.

2. APLASTIC ANEMIA:

Aplastic anemia is a blood disorder in which the body's bone marrow doesn't make enough new blood cells. This may result in a number of health problems including arrhythmias, an enlarged heart, heart failure, infections and bleeding.

Aplastic anemia is a rare but serious condition. It can develop suddenly or slowly and tends to worsen with time unless the cause is found and treated.

3. HAEMOLYTIC ANEMIA:

Haemolytic anemia is a condition in which red blood cells are destroyed and removed from the bloodstream before their normal lifespan is up. A number of diseases, conditions and factors can cause the body to destroy its red blood cells. Haemolytic anemia can lead to

various health problems such as fatigue, pain, arrhythmias, an enlarged heart and heart failure.

There are many types of hemolytic anemias – some of which are inherited and others that are acquired.

INHERITED HAEMOLYTIC ANEMIAS	ACQUIRED HAEMOLYTIC ANEMIAS
• Sickle cell anemia	• Immune haemolytic anemia ○ Autoimmune haemolytic anemia ○ Alloimmune haemolytic anemia ○ Drug-induced haemolytic anemia
• Thalassaemias	• Mechanical hemolytic anemias
• Hereditary spherocytosis	• Paroxysmal nocturnal hemoglobinuria
• Hereditary elliptocytosis	• Certain infections and substances can also damage red blood cells and lead to hemolytic anemia.
• Glucose-6-phosphate dehydrogenase (G6PD) deficiency	
• Pyruvate kinase deficiency	

4. THALASSAEMIA:

Thalassaemias are inherited blood disorders which cause the body to make fewer healthy red blood cells and less hemoglobin (an iron-rich protein in red blood cells).

The two major types of thalassemia are alpha- and beta thalassemia. The most severe form of alpha thalassemia is known as alpha thalassemia major or hydrops fetalis, while the severe form of beta thalassemia is known as thalassemia major or Cooley's anemia.

Thalassaemias affect both males and females and occur most often in people of Italian, Greek, Middle Eastern, Asian, and African descent. Severe forms are usually diagnosed in early childhood and are lifelong conditions.

5. SICKLE CELL ANEMIA:

Sickle cell anemia is a serious disease in which the body makes sickle-shaped ("C"-shaped) red blood cells. Normal red blood cells are disk-shaped and move easily through your blood vessels. Red blood cells contain the protein hemoglobin (an iron-rich protein that gives blood its red color and carries oxygen from the lungs to the rest of the body).

Sickle cells contain abnormal hemoglobin that causes the cells to have a sickle shape, which doesn't move easily through the blood vessels – they are stiff and sticky and tend to form clumps and get stuck in the blood vessels.

The clumps of sickle cells block blood flow in the blood vessels that lead to the limbs and organs. Blocked blood vessels can cause pain, serious infections, and organ damage.

In sickle cell anemia, a lower-than-normal number of red blood cells occur because sickle cells don't last very long. Sickle cells usually die after about 10 to 20 days and the body can't reproduce red blood cells fast enough to replace the dying ones, which causes anemia.

6. ANEMIA CAUSED BY OTHER DISEASES:-

Some diseases can affect the body's ability to make red blood cells. For example, some patients with kidney disease develop anemia because the kidneys are not making enough of the hormone erythropoietin to signal the bone marrow to make new or more red blood cells. Chemotherapy used to treat various cancers often impairs the body's ability to make new red blood cells, and anemia often results from this treatment.

i. PERNICIOUS ANEMIA:

Pernicious anemia is a condition in which the body can't make enough healthy red blood cells because it doesn't have enough vitamin B_{12} (a nutrient found in certain foods). People who have pernicious anemia can't absorb enough vitamin B_{12} due to a lack of intrinsic factor (a protein made in the stomach). However, other conditions and factors can also cause vitamin B_{12} deficiency.

ii. FANCONI ANEMIA:

Fanconi anemia, or FA, is a rare, inherited blood disorder that leads to bone marrow failure. FA is a type of aplastic anemia that prevents your bone marrow from making enough new blood cells for your body to work normally[10]. FA can also cause your bone marrow to make many abnormal blood cells. This can lead to serious health problems, such as leukemia.

FA is a blood disorder, but it can also affect many of the body's organs, tissues, and systems. Children who inherit FA are at higher risk of being born with birth defects, and people who have FA are at higher risk of some cancers and other serious health problems.

FA is an unpredictable disease. The average lifespan of people with FA is between 20 and 30 years. The most common causes of death related to FA are bone marrow failure, leukemia, and solid tumors.

ANEMIA IN PREGNANCY AND POSTNATALLY:

Anemia is the most common medical disorder in pregnancy. Anemia in pregnancy is associated with high maternal morbidity and mortality. Pregnancy causes 2-3 fold increase in requirement of iron and 10-20 fold increase in folate requirement[11]. In iron deficiency anemia, there is a shortage of iron stores (low ferritin), reduced transport and functional iron (low transferrin) limiting red cell production (low Hb) (Table 2).

Table 2

CAUSES OF ANEMIA IN THE NEWBORN	CAUSES OF ANEMIA IN WOMEN (PREGNANCY & LACTATING MOTHERS)
• Blood loss • Decreased RBC production • Increased RBC turnover.	• Inadequate intake of iron rich foods • Excess consumption of coffee/tea • Chronic infections like malaria, TB • Inadequate intake of folate. • Inadequate intake of Vitamin B_{12}. • Worm infestation • Menstrual loss of blood • Low bio-availability of iron in food

Table 3: SEVERITY OF ANEMIA

Sr. No.	Hb LEVEL	CLASSIFICATION
1	<4gm /dl	Very severe
2	4-6.9gm/dl	Severe
3	7-9.9gm/dl	Moderate
4	0-0.9gm/dl	mild

Table 4: DAILY IRON REQUIREMENTS FOR INFANTS AND YOUNG CHILDREN

Sr. No.	AGE	SOURCE	DAILY IRON REQUIREMENT
1	Up to 4 to 6 months (full-term infants)	Breast milk or iron-fortified formula	0.27 mg
2	4 to 6 months to 1 year (full-term infants)	Breast milk or formula plus iron-rich foods*	11 mg
3	1 month to 1 year (premature or low–birth-weight infants)	Iron-fortified preterm formula or iron supplementation (2 mg per kg per day) plus breast milk and iron-rich foods	2 to 4 mg per kg
4	1 to 3 years	Iron-rich foods	7 mg

Table 5: BUILDING A GLOBAL COMMITMENT TO NUTRITION RELATED TO ANEMIA:

YEAR	GLOBAL COMMITMENT TO NUTRITION
2011	The United Nations releases a political declaration on noncommunicable diseases (NCDs) as the outcome of a High-Level Meeting on the Prevention and Control of NCDs.
2012	At the World Health Assembly, national governments adopt a series of nutrition targets as part of the Comprehensive Implementation Plan on Maternal, Infant, and Young Child Nutrition.
2013	The governments of the United Kingdom and Brazil together with the Children's Investment Fund Foundation co-host a summit designed to raise commitment to actions to achieve the Global Targets on Maternal, Infant, and Young Child Nutrition. At the World Health Assembly, national governments adopt a series of targets on the prevention and control of NCDs, including nutrition-relevant targets.
2014	The United Nations holds a follow-up meeting to the 2011 High-Level Meeting on the Prevention and Control of NCDs to review progress. Countries make clear commitments to, by 2015, set national NCD targets for 2025 and establish process indicators taking into account the nine NCD targets.
2014	Governments come together at the Food and Agriculture Organization/World Health Organization International Conference on Nutrition (ICN2) and agree on a set of 10

	commitments in the Rome Declaration on Nutrition and the accompanying Framework for Action.
2015	Countries assemble at the United Nations to adopt a new nutrition target as part of the Sustainable Development Goals to, by 2030, end all forms of malnutrition.
2016	The United Nations General Assembly declares a Decade of Action on Nutrition from 2016 to 2025. The Decade of Action would translate the ICN2 commitments into coherent and coordinated actions and initiatives by all national governments, both low and high income.
2016	Proposed date for the Nutrition for Growth (N4G) Summit in Rio de Janeiro, Brazil 2016 Japan's leadership on nutrition is growing in advance of the 2016 Group of 7 meeting and the lead-up to the 2020 Tokyo Olympics and Paralympics.

DISCUSSION:

WHO regional estimates generated for preschool-age children and pregnant and non-pregnant women indicate that the highest proportion of individuals affected are in Africa (47.5–67.6%), while the greatest number affected are in South-East Asia[12] where 315 million (95% CI: 291–340) individuals in these three population groups are affected. Globally, anemia affects 1.62 billion people (95% CI: 1.50–1.74 billion), which corresponds to 24.8% of the population (95% CI: 22.9–26.7%). The highest prevalence is in preschool-age children (47.4%, 95% CI: 45.7–49.1), and the lowest prevalence is in men (12.7%, 95% CI: 8.6–16.9%). However, the population group with the greatest number of individuals affected is non-pregnant women[13] (468.4 million, 95% CI: 446.2–490.6).In 2014, approximately 15 percent of adults reported difficulty with hearing. Because iron deficiency anemia (IDA) is a common and easily correctable condition, further understanding of the association between IDA and all types of hearing loss may help to open new possibilities for early identification and appropriate treatment. For this study, using data obtained from de-identified electronic medical records from the Penn State Milton S. Hershey Medical Center in Hershey, Pa., iron deficiency anemia was determined by low hemoglobin and ferritin levels for age and sex in 305,339 adults ages 21 to 90 years; associations between hearing loss and IDA were evaluated. Severe anemia, but not red blood cell transfusions, is associated with an increased risk for a potentially fatal intestinal condition in premature infants. The condition called necrotizing enterocolitis is a leading cause of death in very-low-birth-weight infants says first author Ravi[14]Mangal Patel, MD, MSc, assistant professor of pediatrics at Emory University School of Medicine and a neonatologist at Children's Healthcare of Atlanta. Fanconi anemia is a rare genetic disease characterized by hematologic symptoms and high cancer risk. Mutations in nearly 20 different genes have been identified in patients with Fanconi anemia.

Medical researchers now reveal a new Fanconi anemia gene, $RFWD_3$ that is involved in complex DNA repair processes and may also play a relevant role in cancer risk. At the national level, a workshop was organized at the National Institute of Health and Family Welfare, by the Government of India on 6 February 2008. Technical experts from the country and international agencies attended this meeting and recommended specific actions that re-emphasized the universal supplementation of IFA syrup among young children[15].

CONCLUSION:

Anemia in any form is harmful and the consequences that are discussed are applicable to all types of anemia. However, all types of anemia are not manageable in the same manner, and the genetic causes of anemia, like thalassemia or sickle-cell anemia need to be attended to differently and the expected results of the interventions will be different and relatively lesser and slower than iron-deficiency anemia interventions. WHO / UNICEF / UNU strongly advocate that when there is a frequency of anemia above 40%, a universal supplementation is required and it is not cost-effective to screen children for anemia. This is in light of the fact that iron deficiency is almost universal when dealing with this magnitude of anemia. We need to emphasize, train, support, and effectively monitor the program's implementation, and systematically and realistically plan out logistics, supply, monitoring, and implementation of the program at the regional, national, state, and district levels. Only then will this bother of children, that is, anemia, be adequately controlled and the fruits that the program promises will actually be delivered.

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