10.5005/jp-journals-10065-0024

REVIEW ARTICLE

Clinical Evaluation of Different Types of Anemia

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ABSTRACT

Anemia, defined as a hemoglobin level two standard deviations below the mean for age, is prevalent among infants and children as well as adults worldwide. The evaluation of an individual with anemia should begin with a thorough history and risk assessment. Characterizing the anemia as microcytic, normocytic, or macrocytic based on the mean corpuscular volume (MCV) will aid in the work-up and management. Microcytic anemia due to iron deficiency is the most common type of anemia in children. Iron deficiency anemia, which can be associated with cognitive issues, is prevented and treated with iron supplements or increased intake of dietary iron. This review article discusses the clinical evaluation of different types of anemias based on the findings of clinical examination (i.e., pallor, pedal edema, nail changes, and epithelial changes) as well as the results of various investigations such as routine blood investigations (hemoglobin, mean cell hemoglobin concentration [MCHC], packed cell volume, etc.), peripheral smear examination, bone marrow examination, etc. Management options for various types of anemia are different and have been briefly discussed in this article.

Keywords: Anemia, Hemoglobin, Iron deficiency, Mean cell hemoglobin concentration, Megaloblastic, Pallor.

How to cite this article: Saxena R, Chamoli S, Batra M. Clinical Evaluation of Different Types of Anemia. World J Anemia 2018;2(1):26-30.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Anemia is a condition of reduction in the hemoglobin (Hb) concentration of the peripheral blood below the normal level in relation to age and sex.[1] However, it should be remembered that anemia per se is not a disease by itself, but an expression or sign of an underlying disease. The World Health Organization (WHO)[2,3] criteria for anemia in men is <13 gm/dL and women is <12 gm/dL. However, it differs by age, sex, and pregnancy status as shown in Table 1.

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Table 1: World Health Organization criteria for anemia

	Venous blood (gm/dL)	*MCHC*
Adult males	13	34
Adult females, nonpregnant	12	34
Adult females, pregnant	11	34
Children (6 months–6 years)	11	34
Children (6–14 years)	12	34

CLASSIFICATION OF ANEMIA

The classification of anemia based on two factors (Table 2):

1. Red cell morphology
2. Etiology of anemia

Anemia Classification Based on Morphology

Anemia can be classified based on morphology as:

- Normocytic normochromic (MCV 76–96 fL, MCHC 30–35 gm/dL): It is observed in acute blood loss, liver disease, endocrinopathy, anemia of infections, etc.
- Macrocytic (MCV >96, MCHC 30–35 gm/dL): It is observed in vitamin B12 and folic acid deficiency, etc.
- Microcytic (MCV <76 fL, MCHC 30 gm/dL): It is observed in iron deficiency anemia, thalassemia, sideroblastic anemia, pyridoxine deficiency, etc.

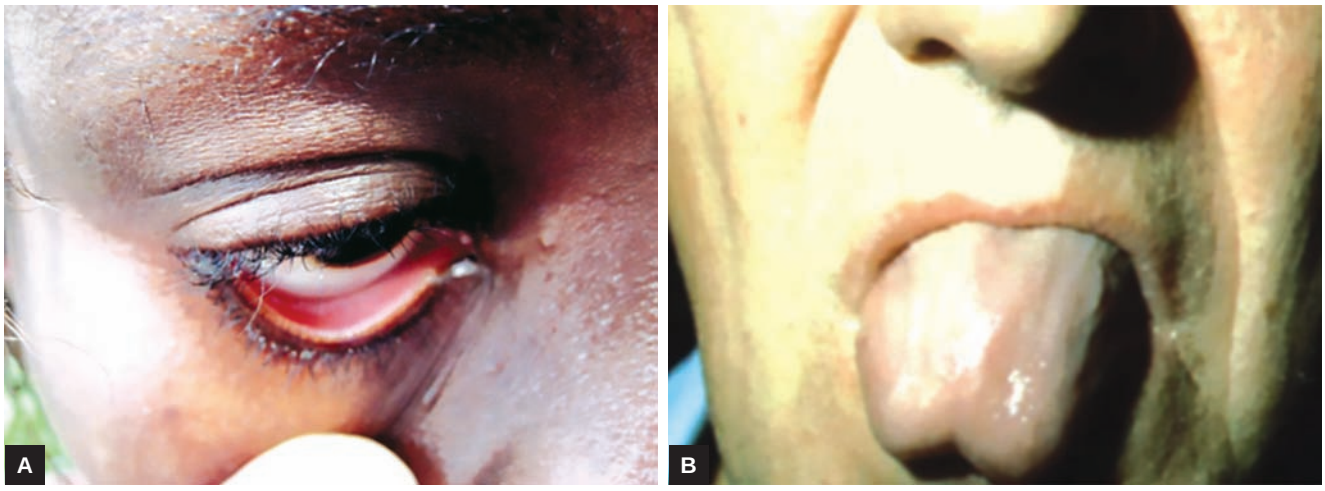
Anemia Classification Based on Etiology

- Anemia due to blood loss:
  - Acute loss: It may be external (e.g., as after trauma or obstetric hemorrhage) and internal [e.g., as bleeding from gastrointestinal (GI) tract, rupture

Table 2: Cytometric classification of anemia

Types	*Lab values*	*Causes*
Macrocytic normochromic anemia	Increased MCV, normal MCHC	Vitamin B12 deficiency
	MCV > 100 fL	Folate deficiency
	MCHC 34	
Microcytic hypochromic anemia	Low MCHC	Thalassemias; iron deficiency anemia; anemia of chronic disease (rare cases)
	Low MCV	
	MCV < 80 fL	
	MCHC < 30	
Normocytic normochromic anemia	Normal MCHC	Anemia due to chronic disease, anemia of acute hemorrhage; aplastic anemias; hemolytic anemias
	Normal MCV	
	MCV > 80–99 fL	
	MCHC 34	

MCV: Mean corpuscular volume



Figs 1A and B: (A) Pallor in the lower palpebral conjunctiva. (B) Pale tongue

of spleen, ruptured ectopic pregnancy, and subarachnoid hemorrhage].
  - Chronic loss: It could be due to worm infestation, menses, repeated blood donation, repeated phlebotomy as treatment of polycythemia vera, etc.
- Hemolytic anemia due to destruction of red blood cells (RBCs)
- Impaired RBC production
  - Defective proliferation and differentiation of stem cells
- Aplastic anemia
- Chronic renal failure
- Endocrinopathy (defective production of hormones of pituitary, thyroid, suprarenal glands, testis)
- Defective proliferation and maturation of differentiation of the blasts:
  - Defective deoxyribonucleic acid (DNA) synthesis: Vitamin B12, folic acid deficiency
  - Defective Hb synthesis:
    - Heme: Iron deficiency, pyridoxine deficiency
    - Globin: Thalassemia and hemoglobinopathies
    - Sideroblastic anemia
    - Anemia of chronic disease: Infections, inflammation, neoplasms
  - Myelophthisis due to infiltration of bone marrow[4]

DIAGNOSIS OF A CASE WITH ANEMIA

The following signs can be observed on general physical examination in patients with anemia.

Pallor

Reduced amount of oxygenated hemoglobin in anemic individuals results in the development of nonspecific pallor of the mucous membranes. Clinical examination may reveal pallor in lower palpebral conjunctiva (Fig. 1A), pale nails, pale palmar surface of hands, pale tongue (Fig. 1B), lips, nail beds, etc.

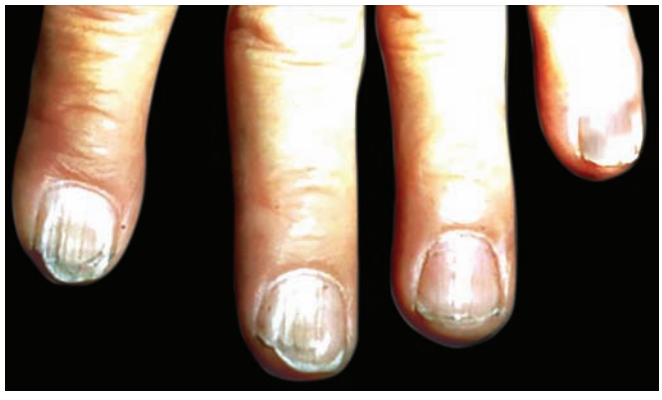


Fig. 2: Koilonychia

Epithelial Changes

The epithelial tissues of nails, tongue, mouth, hypopharynx, and stomach are affected, resulting in development of brittle, which can also develop. Angular stomatitis, characterized by development of ulcerations or fissures at the corners of the mouth, is a less specific sign of anemia. It is commonly associated with deficiency of riboflavin or pyrixodine.

Nail Changes

Thinning, flattening, and finally development of concave spoon-shaped nails, also known as koilonychias (Fig. 2).

Pedal Edema

In severely anemic cases, there may be pedal edema (Fig. 3).

Plummer–Vinson Syndrome

This syndrome is also known as Paterson–Brown–Kelly syndrome after the names of its discoverers. This is a rare

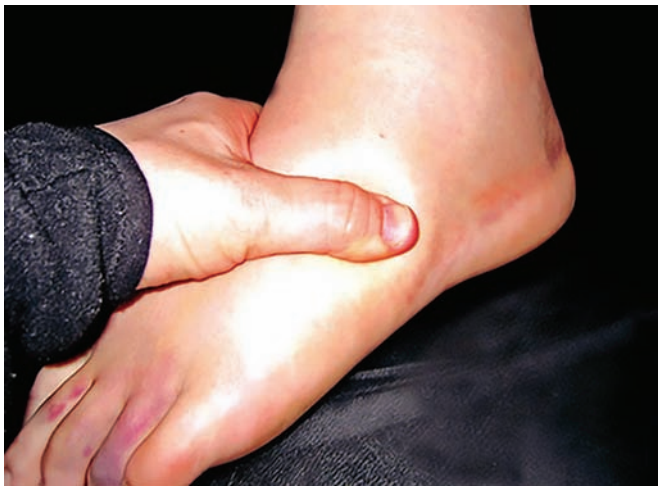


Fig. 3: Pedal edema

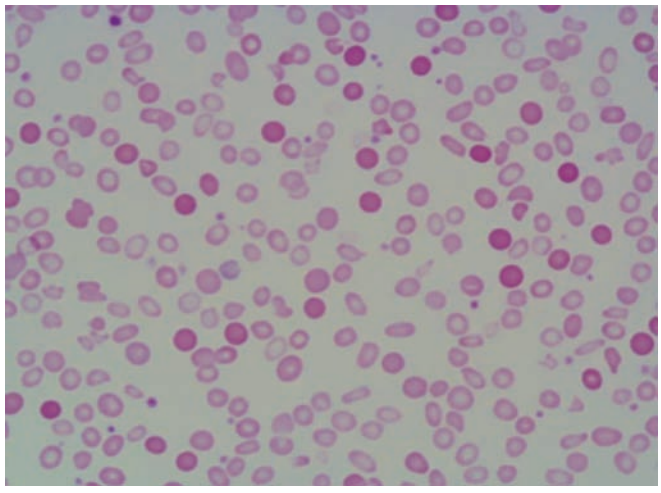


Fig. 4: Peripheral smear in case of iron deficiency anemia

condition characterized by the presence of iron deficiency anemia, nail abnormalities, and dysphagia. Some of the symptoms for Plummer-Vinson syndrome include the following: Pain in the throat during swallowing, burning sensation during swallowing, sensation of food being stuck in larynx, fatigue, pallor, difficulty in swallowing, development of mucosal webs in esophagus, etc.

DIAGNOSIS AND INVESTIGATIONS

The diagnosis of anemia needs to be carried out by various investigations.

Routine Investigation

Routine investigation includes complete blood count with white blood count, platelet count, and red blood count parameters (MCV/mean corpuscular hemoglobin/MCHC), and reticulocyte count.

Peripheral Smear

Peripheral smear examination is another simple method for diagnosis of anemia. Examination of the peripheral smear is an important part of the work-up of patients with anemia.

Peripheral Smear in Iron Deficiency Anemia

Peripheral smear of blood shows microcytic and hypochromic picture. There is presence of pale looking RBCs with large central vacuoles (hypochromic RBCs). The peripheral smear (Fig. 4) shows the following:

- Anisocytosis (abnormal size of cells): The RBCs are small and deformed (microcytosis). The microcytosis is apparent near the smear long before the MCV is decreased after an event producing iron deficiency anemia.
- Poikilocytosis (abnormal shape of cells): Presence of pencil cells and target cells.
- Presence of ring or pessary cells with central hypochromia (large central vacuoles).
- RBC osmotic fragility is slightly reduced.
- Radiochromium-51Cr studies show reduced RBC life span.

Peripheral Smear in Megaloblastic Anemia

- Presence of macrocytes and megaloblasts.
- Hypersegmentation of neutrophils (Fig. 5).
- Fully hemoglobinized RBCs.

Peripheral Smear in Hemolytic Anemia (Thalassemia)[5]

Presence of polychromatic, stippled, and target cells (Fig. 6). Platelets usually are increased in this disorder.

Peripheral Smear in Combined Folate and Iron Deficiency

The peripheral smear in these cases reveals a population of macrocytes mixed among the microcytic hypochromic cells. This combination can normalize MCV.

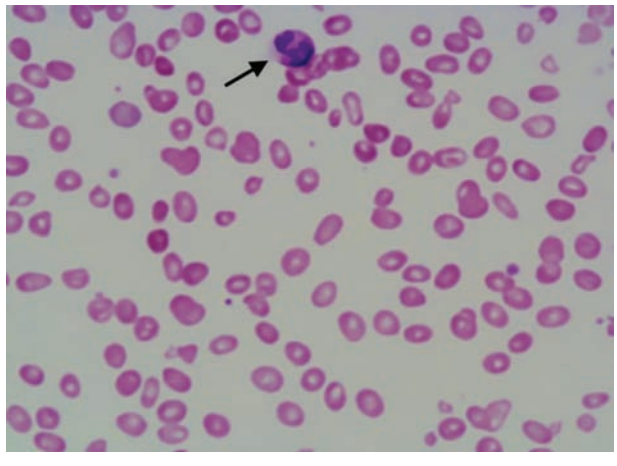


Fig. 5: Peripheral smear in case of megaloblastic anemia. The arrow is pointing toward hypersegmented neutrophil

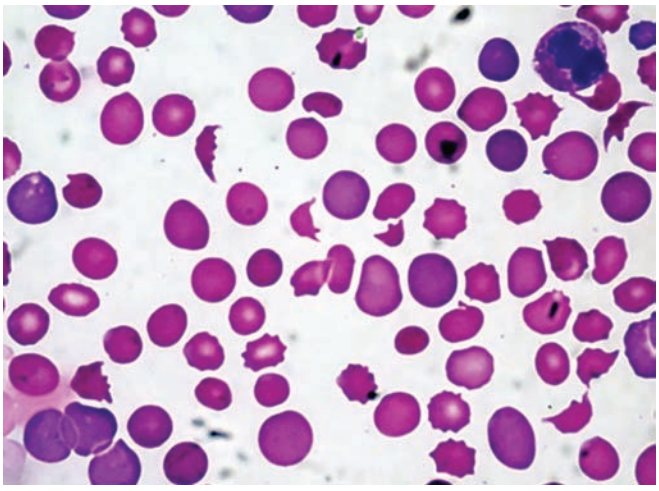


Fig. 6: Peripheral smear in case of hemolytic anemia

Bone Marrow Examination

It may reveal:

- Primary marrow disease (e.g., aplastic anemia and myelodysplastic anemia)
- Marrow involvement of nonmarrow diseases (e.g., lymphoma, infection)
- The bone marrow is used to accurately gauge iron stores and nonmalignant marrow processes (e.g., hemophagocytic syndromes, Gaucher diseases)

Bone marrow examination is indicated in the following cases:

- RBC transfusions
- In case of unexplained anemia, macrocytosis, thrombocytopenia, neutropenia, and splenomegaly
- Unexplained constitutional symptoms as:
  - Fever
  - Chills
  - Early satiety
  - Bone pains
  - Weight loss

Special Investigations

The following are the special investigations needed to make diagnosis and required for specific type of anemia:

- In case of iron deficiency anemia [decreased serum iron, increased total iron-binding capacity (TIBC), decreased bone marrow, and decreased serum ferritin]: It includes serum ferritin level of <12 ng/mL and is highly specific for iron deficiency anemia, serum iron, TIBC, fecal occult blood test, urine analysis for blood, colonoscopy, upper GI endoscopy, small bowel study, and anti-tissue transglutaminase antibodies.
- In case of hemolytic anemia (increased indirect bilirubin, decreased serum haptoglobin, increased lactate dehydrogenase [LDH] levels): It includes indirect bilirubin, serum haptoglobin, direct and indirect Coombs test, urine Hb, urine hemosiderin, LDH, and osmotic fragility and screening for glucose-6-phosphate dehydrogenase deficiency. Peripheral blood film for red cell morphology (may show sickle cell anemia).
- In case of macrocytic anemia: Investigation of vitamin B_{12}[6] (level of <200 pg/mL is diagnostic of megaloblastic anemia), folate (<2 ng/mL is diagnostic of folate deficiency), and reticulocyte count.
  - The following are the investigations to rule out:
    - Spurious cause (e.g., hypertriglyceridemia or cold agglutinin disease)
    - Marrow disease (e.g., myelodysplastic syndromes, serum homocysteine level, and serum methylmalonic acid levels)
- In case of anemia of chronic disease (Normal to increased serum iron, increased ferritin, decreased TIBC, and increased bone marrow iron): It includes erythrocyte sedimentation rate/Mantoux test, chest X-ray (to rule out tuberculosis), C-reactive protein, rheumatoid arthritis factor, anticyclic citrullinated peptides antibodies (to rule out rheumatoid arthritis), antinuclear antibody, antihistone antibodies, antidouble-stranded DNA antibodies (to rule out systemic lupus erythematosus), hepcidin level, serum erythropoietin levels (to rule out chronic kidney disease), and thyroid-stimulating hormone (to rule out hypothyroidism).[7]

MANAGEMENT OF ANEMIA

The treatment for anemia is described below.

Treatment of Iron Deficiency Anemia[8]

- Oral and parenteral iron preparations (ferrous sulfate, ferrous fumarate, and ferrous gluconate).
- In asymptomatic patients, oral iron is adequate; up to 300 mg elemental iron/day can be given depending on patient's requirement.
- Intravenous iron is indicated in:
  - Unable to tolerate oral iron
  - In relatively acute need
  - Absorption deficit
  - In patients with persistent need, like due to ongoing GI bleed

The amount of iron needed can be calculated using the following formula:

$$\text{BW (kg)} \times 2.3 \times (15\text{-patients Hb}) + 500 \text{ or } 1000 \text{ for reduced iron stores}$$

Treatment of Megaloblastic Anemia[9]

Treatment is managed by using oral and intravenous B_{12} and folic acid therapy to correct deficit and replace body stores. It includes:

- The two preparations of B_{12} available are hydroxyl and cyanocobalamin (100–1000 µg given daily for 2 weeks,

then weekly until hematocrit values are normal, then monthly for life).
- Folic acid 3 to 5 mg orally daily

Treatment of Anemia in Chronic Kidney Disease[10]

Treatment is managed by erythropoietin; it is indicated when hemoglobin is <10 gm/dL. Erythropoietin-stimulating agents are:
- Epoetin-alfa (Eposis)
- Darbepoetin-alfa (Aranesp, Cresp)

The adverse effects are: hypertension, thrombosis, and increased risk of malignancy.

Treatment of Aplastic Anemia[11]

The treatment of choice in young adults is bone marrow transplantation. It includes:
- In elderly, immunosuppression with antithymocyte globulin and cyclosporine.
- Androgens oxymetholone 2 to 3 mg/kg orally.

Treatment of Anemia of Chronic Diseases[12]

- Erythropoietin[13] is the treatment of choice at the dose 50 to 150 U/kg three times a week subcutaneously.
- The dose needed for anemia in patients with cancer is up to 300 U/kg.

INDICATIONS OF BLOOD TRANSFUSION[14]

- Anemia:
  - When Hb <7 gm/dL in asymptomatic patients
  - When Hb <10 gm/dL in cases of increased risk of ischemia (i.e., ischemic heart disease, pulmonary disease)
- Major surgical operations
- Predetermined therapeutic programs, such as bone marrow suppression (i.e., paroxysmal nocturnal hemoglobinuria and aplastic anemia)
- Severe burn victims
- Cancer patients requiring therapy
- Women in childbirth and newborn babies in certain cases
- Symptomatic anemia leads to:
  - Tachycardia
  - Mental state changes
  - Angina/electrocardiogram changes of ischemia
  - Shortness of breath, light-headedness, and dizziness on mild exertion

CONCLUSION

Anemia is not a standalone disease but a clinical condition seen in general practice. A detailed history and careful examination are the most common step to make the diagnosis. During investigations, one should try to interpret simple investigations (like complete blood count with general blood picture and other indices) before moving on to high-end investigation. During management of anemia, the cause should be managed first along with the replacement of deficiency of iron or vitamins. Pattern of anemia needs to be recognized, whether it is acute developing or insidious in onset and needs to be managed accordingly.

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