2nd lecture in Hematology by Dr.Alaa Fadhil Alwan

Introduction and Approach to Anemia

Anemia is defined clinically as a blood hemoglobin or hematocrit value that is below the appropriate reference range for that patient. The reference range is derived from the hemoglobin or hematocrit values of a group of persons who are presumed to be without hematologic disease (in other words, normal). It is defined as the range of values containing 95% of the population (two standard deviations above and below the median value). The reference range needs to be adjusted for the age and sex of the patient since the hemoglobin and hematocrit vary with age and sex (in adults). It should also be adjusted for other factors, such as altitude (the normal range for Basrah, muthana, would be different from that for Sulaymaniyah, Duhok).However, for general purposes, anemia can be defined as hemoglobin values less than 14 g/dL (140 g/L) in adult men and less than 12 g/dL (120 g/L) in adult women.
It should always be kept in mind that anemia is not a diagnosis; it is a laboratory abnormality that requires explanation.

CLASSIFICATION OF ANEMIA

Anemia can be approached from two ways: morphologic and pathophysiologic

Morphologic Approach

The morphologic approach to anemia begins with review of the CBC, particularly the mean corpuscular volume (MCV), and the peripheral blood smear. The initial distinction is based on the red cell size: anemias are classified as microcytic, normocytic, or macrocytic. The presence of abnormally shaped erythrocytes (poikilocytes) may suggest a specific disease or cause.

Classification of Anemia Based on Erythrocyte Size

1. Microcytic: e.g. IDA, Sideroblastic anemia, Thalassemia
2. Normocytic: e.g. Anemia of chronic disease, Anemia of renal disease,
3. Macrocytic: e.g Megaloblastic anemia due to folate or cobalamin, Hemolytic anemia (reticulocytosis) Hypothyroidism , Myelodysplastic syndrome

Pathophysiologic (Functional or Kinetic) Approach

The pathophysiologic approach1 is based primarily on the reticulocyte count. Anemias are classified into three broad categories: 1.hemorrhagic/hemolytic (hyperproliferative) anemias, 2. hypoproliferative anemias, and 3. maturation defects,

1. hemorrhagic/hemolytic (hyperproliferative) anemias, there is increased destruction or loss of erythrocytes. The bone marrow is attempting to respond to the anemia and is producing mature erythrocytes but is unable to fully compensate for the increased red cell loss. The reticulocyte production index is high (>3) and the MCV is frequently high since reticulocytes are larger than normal mature erythrocytes.e.g Acute blood loss, Acute hemolysis: Intravascular or Extravascular, and Chronic hemolysis

2. Hypoproliferative anemias, the marrow fails to appropriately respond to the anemia, but the cells that are produced are usually normal. The reticulocyte count or reticulocyte production index is low; erythrocyte morphology is unremarkable.e.g IDA , Chronic renal disease and Endocrine disorders

3. Maturation defect anemias, the bone marrow is attempting to respond to the anemia, but the cells produced are unable to enter the circulation and most die within the bone marrow (ineffective erythropoiesis). The reticulocyte count is low, and, in contrast to the hypoproliferative anemias, erythrocyte morphology is abnormal. The maturation defect anemias are sub classified into cytoplasmic maturation defects, which are generally associated with microcytic erythrocytes, and nuclear maturation defects, which are associated with macrocytic erythrocytes.

SYMPTOMS AND SIGNS OF ANEMIA

Common symptoms of anemia include decreased work capacity, fatigue, weakness, dizziness, palpitations, and dyspnea on exertion. The severity of symptoms may vary widely depending on the degree of anemia, the time period over which anemia developed, the age of the patient, and other medical conditions that are present. If the anemia developed gradually (months or years), compensatory mechanisms such as an expanded plasma volume and increased 2, 3-diphosphoglycerate (2, 3-DPG) have time to take effect. Consequently, the patient may not experience any symptoms with a hemoglobin level down to 8 g/dL, or even lower. If the anemia developed more rapidly, the patient may note symptoms with a hemoglobin level as high as 10 g/dL. Children may tolerate remarkably low hemoglobin levels with few symptoms, whereas older patients with cardiovascular or pulmonary disease tolerate even mild anemia poorly. Angina pectoris may be the initial symptom of anemia in patients with coronary atherosclerosis. Physical signs of anemia include pallor, tachycardia, increased cardiac impulse on palpation, systolic “flow”murmur heard at the apex and along the left sternal border, and a widened pulse pressure (increased systolic blood pressure with a decreased diastolic blood pressure). Pallor is best noted in the conjunctiva, mucous membranes, palmar creases, and nail beds, especially in people with darkly pigmented skin.

GENERAL APPROACH TO A PATIENT WITH ANEMIA

Clinical History:

Questions	**significance**
Onset of symptoms: insidious or abrupt	Nutritional deficiency likely to be insidious in onset; hemolysis more likely to be abrupt
Duration of symptoms	Nutritional deficiency is likely to be of longer duration; hemolysis is more likely to be rapid
Previous CBC? When and What circumstances?	A previous normal CBC helps exclude an Inherited disorder
Previous diagnosis of anemia? When and what circumstances?	Possible recurrence of previous disease

Family history of anemia?	Possible inherited hemoglobinopathy,thalassemia, membrane defect or enzyme deficiency
Change in bowel habits? Black or tarry stools? Hematochezia?	Iron loss due to peptic ulcer disease, colon carcinoma, or other GI tract malignancy; malabsorption in folate or B12 deficiency
Diet: meats, dairy products, fresh fruits and vegetables	Does the patient have adequate intake of iron (meat), folic acid (fresh fruits and vegetables),
Medications	Interference with folate metabolism (sulfa drugs, trimethoprim, antiepileptic medications); oxidant drugs causing hemolysis in enzyme deficiency; blood loss from gastritis or peptic ulcer due to nonsteroidal anti-inflammatory drugs
Past medical history	Anemia of chronic disease due to inflammatory diseases or malignancy; decreased erythropoietin production in renal disease
Alcohol consumption	Alcohol interferes with folate metabolism; liver disease
Menstrual history (women)	Iron loss in menorrhagia
Reproductive history (women)	Iron loss in pregnancy
Occupational history	Exposure to chemicals that are toxic to bone marrow (organic solvents, hydrocarbons)
Jaundice or dark urine	Hyperbilirubinemia could indicate hemolysis or ineffective erythropoiesis
Weight loss	Common with malignancies
Fevers, night sweats	Common in malignancies; could indicate chronic infection
Abdominal discomfort or liver Fullness	Splenomegaly occurs with lymphoma, chronic disease, myeloproliferative disorders
Sores in mouth or sore tongue	Common in megaloblastic anemia; may also occur in iron deficiency
Paresthesias, clumsiness, weakness	Neurologic disease due to B12 deficiency

Physical Examination

System	Significance
General appearance	pallor, Jaundice due to hemolysis or megaloblastic anemia; cachexia; tremor or myxedema due to thyroid disease;"spider" angiomata in liver disease; "spoon nails" in iron deficiency
Eye examination	pallor, Scleral icterus due to hemolysis; retinal hemorrhages in iron deficiency and other anemias
Head and neck	Glossitis or angular stomatitis in iron deficiency or megaloblastic anemias
Cardiac	Murmurs due to bacterial vegetations in endocarditis; flow murmur in anemia
Abdomen	Splenomegaly in chronic hemolytic anemias; hepatosplenomegaly in lymphoma or myeloproliferative disorder; mass due to intra-abdominal malignancy
Lymphatic system	Lymphadenopathy in lymphoma
Nervous system	Peripheral neuropathy, cerebellar or cortical dysfunction due to cobalamin deficiency

Laboratory Tests

Important laboratory tests include a CBC with erythrocyte indices, white cell count and leukocyte differential, and platelet count. Important chemistries include serum creatinine, calcium, liver profile including total and direct bilirubin, lactic dehydrogenase, total protein, and albumin. A reticulocyte count (corrected for anemia) . additional tests could include iron indices (serum ferritin or serum iron/transferrin/ saturation) , folic acid and cobalamin (vitamin B12) levels, hemoglobin electrophoresis, and direct antiglobulin (Coombs') test.
A general approach to the laboratory diagnosis of the anemic patient is based largely on erythrocyte size (MCV). Naturally, the approach for each individual case will be modified by the history, physical examination, and other clinical and laboratory information for that specific patient.

Evaluation of a Microcytic Anemia (MCV < 80 fL)

The key initial steps in the evaluation of a microcytic anemia are iron indices and examination of a blood smear. The most common cause of microcytic anemia is iron deficiency. If the iron indices confirm the presence of an iron deficiency, the next step is to discover the cause (blood loss, insufficient dietary iron) and begin replacement therapy. If the iron studies do not suggest iron deficiency, the next step is to order a hemoglobin electrophoresis to diagnose thalassemia. Consider the ethnic origin and family history of the patient. A blood smear could be done to check for target cells and basophilic stippling. Complete blood counts and blood smears from relatives might be helpful in this circumstance. Consider the possibility of a chronic inflammatory process that might be causing anemia of chronic disease. If none of

these appear to be responsible for the anemia, a bone marrow examination with an iron stain to look for ringed sideroblasts might be required.

Evaluation of a Macrocytic Anemia (MCV > 100 fL)

The most important initial step in the evaluation of an anemia with an increased MCV is to differentiate megaloblastic anemia from macrocytic, non-megaloblastic anemia. Examine a blood smear for hypersegmented neutrophils and oval macrocytes, which would suggest a megaloblastic anemia. The first laboratory studies should be serum cobalamin, serum folate, and red cell folate levels. If these are all normal, a reticulocyte count should be done to check for a hemorrhagic or hemolytic process. A careful examination of the blood smear may also be helpful; for example, the presence of polychromasia would indicate reticulocytosis, and the presence of target cells would suggest liver disease. If reticulocytosis is confirmed, the underlying hemolytic or hemorrhagic process should be determined. Tests that might be helpful in this circumstance include a direct antiglobulin (Coombs') test, a hemoglobin electrophoresis, and a screen for glucose-6- phosphate dehydrogenase (G6PD) deficiency.

Evaluation of a Normocytic Anemia (MCV 80–100 fL)

The first step in the evaluation of a normocytic anemia is to assess the clinical history. Does the patient have some process that would cause an anemia of chronic disease? Does the patient have renal insufficiency, thyroid disease, or another endocrine disease? Check iron studies and folate/vitamin B12 levels to look for early iron deficiency or combined nutritional deficiency. If the reticulocyte count is increased, follow with hemoglobin electrophoresis to look for a hemoglobinopathy, a screen for G6PD deficiency, and, possibly, a direct antiglobulin test. If the reticulocyte count is low, consider anemia of chronic disease, chronic renal insufficiency, thyroid disease, or marrow damage. If the cause is not apparent, a bone marrow aspirate and biopsy should be done.

Anemia with Increased Reticulocyte Production Index

Anemia in the presence of increased reticulocyte production suggests blood loss (hemorrhage) or increased erythrocyte destruction (hemolysis).
Anemia due to acute or recent hemorrhage will usually be apparent on clinical history and physical examination. Hemolytic anemias will usually fall into one of the following general groups:

- Obvious exposure to infectious, chemical, or physical agents
- Positive direct antiglobulin (Coombs') test (immune hemolytic anemia)
- Spherocytic anemia, but with a negative antiglobulin test (most likely hereditary spherocytosis)
- Hemolytic anemia with specific morphologic abnormalities on blood smear (sickle cells, elliptocytes, schistocytes)
- Miscellaneous conditions including hemoglobinopathies, thalassemias, enzyme defects, metabolic abnormalities, and paroxysmal nocturnal hemoglobinuria