ANEMIA

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Anemia

Definition

Defined as decreasing in circulating RBC mass

Hb < 12 mg/dl or Htc <36% for nonpregnant women

Hb < 13 mg/dl or Htc < 39% in men

Classification

Anemia can be classified into 3 etiologic groups

- Blood loss (acute or chronic)
- Decreased RBC production
- Increased RBC destruction (hemolysis)

Definitions

- Red blood cell indices are blood tests that provide information about the hemoglobin content and size of red blood cells.

- **Mean corpuscular volume (MCV)**

  Normal range: 80–100 fL (femtoliter)

- **Mean corpuscular hemoglobin (MCH)**

  Normal range: 27-31 pg/cell

- **Mean corpuscular hemoglobin concentration (MCHC)**

  Normal range: 32-36 g/dL

- **Red blood cell distribution width (RDW)**

- (RDW) is a measure of the range of variation of red blood cell (RBC) volume, yielding clues about morphology.

Clinical Presentation

Acute anemia

is a sudden and rapid decrease in RBCs, primarily caused by hemolysis or acute hemorrhage

- fatigue, malaise, dyspnea, syncope/presyncope, or angina.

Chronic anemia

is characterized by a gradual decline in RBCs over time

In contrast to acute anemia, patients with chronic anemia are less symptomatic, at times only presenting with fatigue or dyspnea with increased activity or exertion.

patients usually have symptoms when Hgb <7 g/dL.

The following history will aid in the evaluation and management of anemia:

- Gastrointestinal (GI) hemorrhage
- Obstetric and menstrual history
- Comorbidities associated with anemia such as GI surgery or malabsorption,
- Renal disease
- Rheumatologic disease, or other chronic inflammatory conditions
- Family history of anemia
- History of blood donation or prior RBC transfusions
- Prescribed and over-the-counter medicines including supplements, alcohol consumption, diet, ethnic background, and religious beliefs pertaining to blood transfusions
- Symptoms suggestive of other cytopenias such as bruising (thrombocytopenia) or severe or recurrent infections (neutropenia)

Physical Examination

Common signs and symptoms of anemia include

- pallor
- tachycardia
- hypotension
- dizziness
- tinnitus
- headaches
- decreased cognitive ability, fatigue, and weakness

- atrophic glossitis
- angular cheilosis
- koilonychia (spoon nails), and brittle nails are more common in severe, long-standing anemia
- reduced exercise tolerance, dyspnea on exertion, and heart failure
- high-output heart failure and hypovolemic shock may be seen in acute, severe cases.

Diagnostic Testing

Laboratories

- The complete blood count (CBC)
- Reticulocyte count
- Blood film smear
- (RDW): Reflects the variability in the volume of the RBCs. An elevated RDW indicates an increased variability in RBC size, which is a nonspecific but important finding in anemic patients
- The reticulocyte count measures the percentage of immature red cells in the blood and reflects production of RBCs in the bone marrow (BM).

- The peripheral smear

Should be reviewed to assess the morphologic characteristics of RBCs including the shape, size, presence of inclusions, and orientation of cells in relation to each other. RBCs assume many abnormal forms, such as acanthocytes, schistocytes, spherocytes, or tear drop cells, and abnormal orientation such as agglutination or Rouleaux formation. Each is associated with several specific disease processes that may warrant additional evaluation.

Diagnostic Procedures

- A BM biopsy is often indicated in cases of unexplained anemia with a low reticulocyte count or with anemia associated with other cytopenias.

It should be strongly considered if the diagnosis is uncertain and RBC transfusions are required.

ANEMIAS ASSOCIATED WITH DECREASED RBC PRODUCTION

- IDA
- Thalassemia
- Sideroblastic anemia
- Macrocytic / megaloblastic anemia
- Anemia of chronic disease
- Anemia in Cancer patient
- Anemia in HIV
- Aplastic anemia

ANEMIAS ASSOCIATED WITH INCREASED RBC Destruction

- Anemias Associated With Increased Erythropoiesis

(Blood loss and hemolysis)

- Sickle Cell Disease
- Glucose-6-Phosphate Dehydrogenase Deficiency (G6PD)
- Autoimmune Hemolytic Anemia
- Drug-Induced Hemolytic Anemia
- Microangiopathic Hemolytic Anemia

Iron Deficiency Anemia (IDA)

- Iron deficiency

is the most common cause of anemia in the microcytic anemia. The most common causes of iron deficiency anemia are blood loss (e.g., menses, GI blood loss), decreased absorption (e.g., achlorhydria, celiac disease, bariatric surgery, Helicobacter pylori infection), and increased iron demand (e.g., pregnancy). It is important to determine the cause of iron deficiency, and in the absence of menstrual bleeding, evaluation of the GI tract should be performed to identify a potential cause including the possibility of an **occult malignancy.**

DIAGNOSIS

Clinical Presentation:

Patients often present with

- Fatigue or malaise that is typically worsened with activity
- Pica (consumption of substances of no nutritional value such as ice, starch, or clay) occurs in about 25% of patients with chronic IDA and rarely occurs in other clinical settings
- Restless leg syndrome is a common but a nonspecific finding
- Pallor is a common physical finding in patients with IDA but is not specific
- Cold intolerance

Diagnostic Testing

Peripheral blood smear may shows:

- Hypochromia (increased central pallor of RBCs)
- Microcytosis
- Pencil-shaped cells

Laboratories

- Ferritin is the primary storage form for iron in the liver and is a specific marker of an absolute iron deficiency. The reference range is 30–400 ng/mL. A ferritin level of **<10 ng/mL** in women or <20 ng/mL in men almost always reflects low iron stores.
- Ferritin is an acute-phase reactant, so normal levels may be seen in inflammatory states despite low iron stores

A serum ferritin level of >200 ng/mL generally excludes an iron deficiency

Iron, total iron binding capacity (TIBC), and transferrin saturation are often used in combination with ferritin to diagnose iron deficiency anemia. Serum iron level alone is an unreliable indicator given its significant fluctuation after a meal.

Diagnostic Procedures

- BM biopsy that shows

absent staining for iron is the definitive test to diagnose IDA

- An iron challenge can be performed in the absence of response to oral iron replacement to differentiate poor absorption from other causes (e.g., nonadherence or occult blood loss). After an 8-hour fast, a baseline iron is measured immediately followed by oral intake of liquid ferrous sulfate 5 mg/kg given with orange juice or vitamin C-containing beverage. Serum iron is measured again after 90 minutes. Normal iron absorption will result in an increase of serum iron of at least 50 µg/dL and a lower level is indicative of poor absorption

TREATMENT

- **Oral iron therapy**

Iron is best absorbed on an empty stomach, and 3–10 mg of elemental iron can be absorbed daily.

Oral iron ingestion may induce a number of GI side effects, including epigastric distress, bloating, and constipation.

- Ferrous sulfate 325 mg (containing 65 mg elemental iron) commonly prescribed formulation
- Ferrous gluconate 300mg (containing 36 mg elemental iron)
- Ferrous fumarate 100mg (containing 33 mg elemental iron)

In general, patients responding to oral iron therapy should see an increase in reticulocyte count within 1 week of therapy. Treatment should be continued until the total iron deficit is replete

- **Parenteral iron therapy**

There are several formulations of IV iron, and indications for parenteral iron over oral iron include:

- Poor absorption (e.g., inflammatory bowel disease, malabsorption)
- Very high iron requirements that cannot be met with oral supplementation (e.g., ongoing bleeding) Intolerance to oral preparations Functional iron deficiency in chronic kidney disease (CKD)

Thalassemia

- The thalassemia syndromes are inherited disorders characterized by reduced Hgb synthesis associated with mutations in either the α- or β-gene of the molecule

Alpha thalassemia

AA / AA	Normal
AA / A -	Mild microcytosis (Silent Carrier)
AA / - - A - / A -	Mild microcytosis (Trait or Carrier) (cis vs trans)
A - / - -	Hemoglobin H disease- clinically variable
- - / - -	Hydrops Fetalis (Alpha Thal Major)

CLASSIFICATION OF β THALASSEMIA

CLASSIFICATION	GENOTYPE	CLINICAL SEVERITY
β thal minor/trait	β/β+, β/β0	Silent
β thal intermedia	β+ /β+, β+/β0	Moderate
β thal major	β0/ β0	Severe

DIAGNOSIS

- Peripheral smear may show microcytic hypochromic RBCs, along with poikilocytosis and nucleated RBCs
- Hgb electrophoresis is often diagnostic for β-thalassemia showing an increased percentage of Hgb A2 and Hgb F. Silent carriers with a single α-chain loss generally have a normal electrophoresis

Adults with Hgb H disease demonstrate Hgb H (β-tetramers) on electrophoresis. The diagnosis of α-thalassemia is confirmed by α-globin gene analysis

TREATMENT

- Patients with either α- or β-thalassemia trait require no specific treatment.
- In patients with more severe forms of the disease, RBC transfusions to maintain an Hgb level of 9–10 g/dL are needed to prevent the skeletal deformities that result from accelerated erythropoiesis
- In severe forms of thalassemia, repeated transfusions result in tissue iron overload, which may cause congestive heart failure (CHF), hepatic dysfunction, glucose intolerance, and secondary hypogonadism. Chelation therapy is indicated for transfusion-associated iron overload from any cause. It is indicated in patients with a ferritin consistently >1000 ng/mL, which may occur after a transfusion burden of >20 units of packed RBCs

- Stem cell transplantation (SCT) is the only curative therapy and should be considered in young patients with thalassemia major who have HLA-identical donors. Gene therapy is the subject of ongoing research and holds promise
- Splenectomy should be considered in patients with accelerated (more than two units/month) transfusion requirements. To decrease the risk of postsplenectomy sepsis, immunization against pneumococcus, Haemophilus influenzae, and Neisseria meningitidis should be administered at least 2 weeks before surgery if not previously vaccinated. Splenectomy is rarely recommended in patients who are younger than 5–6 years because of the increased risk of sepsis

Sideroblastic Anemias

Sideroblastic anemias are hereditary or acquired RBC disorders characterized by abnormal iron metabolism associated with the presence of ring sideroblasts in the developing RBCs in the BM

Etiology

Acquired Primary sideroblastic anemia (myelodysplastic syndrome [MDS]) Secondary sideroblastic anemia is caused by drugs (i.e., chloramphenicol, cycloserine, ethanol, isoniazid, pyrazinamide), lead or zinc toxicity, chronic ethanol use, or copper deficiency Hereditary X-linked Autosomal Mitochondrial

DIAGNOSIS

A BM examination including cytogenetics is needed to evaluate for the presence of ring sideroblasts or other abnormal marrow forms

TREATMENT

Remove any possible offending agent. Pyridoxine 50–200 mg daily may be effective

Macrocytic/Megaloblastic Anemia

- Etiology

Vitamin B12 deficiency occurs insidiously over several years because daily vitamin B12 requirements are low compared to total body stores

Vitamin B12 deficiency occurs in up to 20% of untreated patients within 8 years of partial gastrectomy and in almost all patients with total gastrectomy or pernicious anemia (PA).

In nonvegan adults, vitamin B12 deficiency is almost always due to malabsorption.

Folate deficiency results from a negative folate balance arising from malnutrition, malabsorption, or increased requirement (pregnancy, hemolytic anemia).Patients on weight-losing diets, alcoholics, the elderly, and psychiatric patients are particularly at risk for nutritional folate deficiency. Folate deficiency may be seen in several settings:

- Pregnancy and lactation in which there is a three- to fourfold increased daily folate requirements.
- Folate malabsorption secondary to celiac disease or bariatric surgery. Drugs that can interfere with folate absorption include ethanol, trimethoprim, pyrimethamine, diphenylhydantoin, barbiturates, and sulfasalazine. Dialysis-dependent patients require more folate intake because of increased folate losses. Patients with hemolytic anemia, such as sickle cell anemia, require increased folate for accelerated erythropoiesis and can present with aplastic crisis (rapidly falling RBC counts) with folate deficiency.

DIAGNOSIS

Clinical Presentation

- In addition to symptoms of anemia, vitamin B12 deficiency may demonstrate neurologic symptoms, such as peripheral neuropathy, paresthesias, lethargy, hypotonia, and seizures. Important physical findings include signs of poor nutrition, pigmentation of skin creases and nail beds, or glossitis.
- Vitamin B12 deficiency may cause decreased vibratory and positional sense, ataxia, paresthesias, confusion, and dementia. Neurologic complications may occur in the absence of anemia and may not fully resolve despite adequate treatment.
- Folic acid deficiency does not result in neurologic disease.

Diagnostic Testing

Laboratories

- Macrocytic anemia and leukopenia and thrombocytopenia may occur.
- The peripheral smear may show macro-ovalocytes; hypersegmented neutrophils (containing six or more nuclear lobes) are common.
- Serum vitamin B12 and folate levels should be measured. RBC folate is a more accurate indicator of body folate stores than serum folate,
- Serum methylmalonic acid (MMA) and homocysteine (HC) may be useful when the vitamin B12 is 100–400 pg/mL (or borderline low as defined by the laboratory reference range). MMA and HC are elevated in vitamin B12 deficiency; only HC is elevated in folate deficiency.

Diagnostic Procedures

- BM biopsy may be necessary to rule out MDS or acute myeloid leukemia because these disorders may present with findings similar to those of megaloblastic anemia including a hypercellular marrow with an accumulation of immature cells

TREATMENT

- **Folic acid** 1 mg PO daily is given until the deficiency is corrected. High doses of folic acid (5 mg daily) may be needed in patients with malabsorption syndromes.

- **Vitamin B12** deficiency is corrected by administering cyanocobalamin. Initial treatment (1 mg/d intramuscular cyanocobalamin) is typically administered in the setting of severe anemia, neurologic dysfunction, or chronic malabsorption. After 1 week of daily therapy, a commonly employed regimen is 1 mg/wk given for 4 weeks and then 1 mg/mo for life.

Anemia of Chronic Disease

Anemia of chronic disease (ACD) often develops in:

- patients with long-standing inflammatory diseases
- malignancy
- autoimmune disorders
- chronic infection

Etiology is multifactorial including:

- defective iron mobilization during erythropoiesis
- inflammatory cytokine-mediated suppression of erythropoiesis
- impaired EPO response to anemia

- Hepcidin is a critical regulator of iron homeostasis and is normally low when iron is deficient, allowing for increased iron absorption and utilization
- Chronic inflammation increases hepcidin levels and causes a functional iron deficiency due to impaired iron recycling and utilization
- Hepcidin is renally cleared, suggesting a role in anemia of chronic renal disease

DIAGNOSIS

- Anemia is normocytic in 75% of cases and microcytic in the remainder of cases
- The soluble transferrin receptor level is helpful in differentiating ACD (normal) and iron deficiency (elevated) when the ferritin is indeterminate
- Measurement of serum hepcidin may become part of the standard evaluation of anemia (when the assay becomes widely available). Iron studies may show low serum iron and TIBC

TREATMENT

- Therapy for ACD is directed toward the underlying disease and eliminating exacerbating factors such as nutritional deficiencies and marrow-suppressive drugs
- Enteral iron is typically ineffective in ACD because of reduced intestinal absorption of iron
- ESA therapy should be considered if the patient is transfusion dependent or has symptomatic anemia.
- ESA therapy is discontinued when the **Hgb is >11 g/dL** to reduce risk of cardiovascular adverse events

Aplastic Anemia

Aplastic anemia (AA)

is a disorder of hematopoietic stem cells that usually presents with pancytopenia. Most cases are acquired and idiopathic, but AA can also arise from an inherited BM failure syndrome such as Fanconi anemia, dyskeratosis congenita, and Shwachman–Diamond syndrome. Approximately 20% of cases may be associated with drug or chemical exposure

- Approximately 10% of cases are associated with viral illnesses (e.g., viral hepatitis, Epstein–Barr virus, cytomegalovirus [CMV]). Clonal hematopoiesis is a feature of AA, with MDS and acute myeloid leukemia (AML) developing in ~15% of patients

DIAGNOSIS

- Diagnostic Criteria AA is a diagnosis of exclusion, and other causes of pancytopenia should be ruled out

TREATMENT

- Treat underling cause
- Patients younger than the age of 50 with severe AA, should be evaluated for eligibility for allogeneic SCT
- Patients over the age of 50 with severe AA or younger patients without SCT donor are treated with eltrombopag 75–150 mg/d along with cyclosporine and antithymocyte globulin (ATG)
- Immunosuppressive treatment with cyclosporine and ATG should be considered in patients with severe AA who do not undergo an SCT.

ANEMIAS ASSOCIATED WITH INCREASED RBC DESTRUCTION

Anemias Associated With Increased Erythropoiesis

- **Blood loss**: any source of bleeding
- **Hemolysis:** can be categorized into two broad groups based on the cause of destruction:
  - **intrinsic** (caused by deficits inherit to the RBC)
  - **extrinsic** (caused by factors external to the RBC)

- In general, intrinsic causes are inherited, whereas extrinsic causes tend to be acquired

(i.e., hereditary spherocytosis, sickle cell disease, G6PD deficiency).

- Extrinsic disorders can result from antibodies (i.e., cold or warm reactive immunoglobulin), or infectious agents (i.e., malaria), trauma, chemical agents (i.e., venom), or liver disease

- Hemolytic disorders are also commonly categorized by the location of RBC destruction:
- intravascular (within the circulation)
- extravascular (within the macrophage in the liver or spleen)

DIAGNOSIS

Laboratory findings of patients with suspected hemolysis typically include:

- Normocytic or macrocytic anemia with an elevated reticulocyte count
- Elevated LDH and indirect hyperbilirubinemia
- Decreased haptoglobin due to binding of intravascular Hgb
- The direct Coombs test (direct antiglobulin testing [DAT]) is an indicator of the presence of antibodies or complement bound to RBC
- The indirect Coombs test indicates the presence of antibody in the plasma

Sickle Cell Disease

SCD is a group of hereditary Hgb disorders in which Hgb undergoes a sickle shape transformation under conditions of deoxygenation

Sickle cell trait has been associated with an increased risk of pulmonary embolism, proteinuria, and CKD. Minimizing other risk factors for kidney disease is likely to benefit patients at risk

CLINICAL PRESENATION

- The most common clinical manifestations of SCD result from hemolysis and/or vascular occlusions
- Vascular occlusions include
  - pain crises
  - avascular necrosis (AVN)
  - priapism
  - acute chest syndrome (ACS)

Whereas hemolytic complications include:

- pulmonary hypertension
- cholelithiasis
- leg ulcers

Strokes and renal medullary infarctions are complications of both

TREATMENT

- Rehydration
- Pain control
- Antibiotic
- Folic acid / transfusion exchange

G6PD Deficieancy

G6PD deficiency represents the most common disorder of RBC metabolism worldwide.

Deficiency of G6PD renders RBCs more susceptible to oxidative damage through decreased glutathione reduction, leading to chronic or acute episodic hemolysis in the presence of oxidative stress

- X-linked inheritance
- G6PD is felt to be protective against malaria, thus accounting for its prevalence in malaria-endemic areas
- Hemolysis is triggered by exposure to mediators of oxidative stress (i.e., drug, infections, and fava beans)

DIAGNOSIS

Diagnosis is determined by measuring G6PD activity in RBCs from a peripheral blood sample

TREATMENT

- In the most common form of G6PD deficiency, hemolytic episodes tend to be self-limiting; the mainstay of treatment is supportive
- The underlying cause of oxidative stress should be addressed (i.e., treatment of infection, removal of drug)

Autoimmune Hemolytic Anemia

(AIHA) results from autoantibodies targeted to antigens on the patient's RBCs, resulting in either extravascular hemolysis (removal of RBC by tissue macrophages in the liver or spleen) or intravascular hemolysis

Classification

There are two main types of AIHA:

- **Warm AIHA**-antibodies interact best with RBCs at 37°C and usually cased bu IgG autoantibody. Idiopathic or (lymphoma , CLL)
- **Cold AIHA** -antibodies interact best with RBCs below 37°C, and usually caused by IgM auto antibody. Due to infecton; mycoplasma, Epstain – Barr, lymphoma or idiopathic

Diagnosis

- The hallmark of diagnosis is by a positive DAT (also known as a direct Coombs test). The DAT detects the presence of IgG or complement in the form of C3 bound to the RBC surface. The typical results for the DAT are shown here:
- **Warm AIHA**: IgG positive and C3 positive or negative
- **Cold AIHA**: IgG negative and C3 positive

TREATMENT

- Treat underlying cause
- Glucocorticoid
- Blood transfusion
- Splenectomy

Drug-Induced Hemolytic Anemia

- Drug-induced hemolytic anemia is anemia resulting from exposure to a medication
- Hemolysis occurs by several mechanisms such as drug-induced antibodies, hapten formation, and immune complexes. The most commonly implicated agents are cephalosporins, penicillins, NSAIDs, and quinine or quinidines

TREATMENT

The initial treatment may be similar to treatment of warm AIHA with corticosteroids if the etiology is unclear, but if drug-induced hemolytic anemia is suspected, the most important treatment is discontinuation of the offending agent

Microangiopathic Hemolytic Anemia

Microangiopathic hemolytic anemia (MAHA) is

a syndrome of traumatic intravascular hemolysis causing fragmentation of the RBCs that are seen on peripheral blood smear (schistocytes)

It is not a specific diagnosis but suggests a limited differential diagnosis

Etiology

Possible causes of MAHA include:

- mechanical heart valve
- malignant hypertension
- vasculitis
- adenocarcinoma
- preeclampsia/eclampsia
- disseminated intravascular coagulation (DIC)
- thrombotic thrombocytopenic purpura (TTP)
- hemolytic-uremic syndrome (HUS)

DIAGNOSIS

MAHA is established by confirming the presence of hemolysis with laboratory data (LDH, haptoglobin, indirect bilirubin) and identifying RBC fragments (schistocytes) on peripheral blood smear. Thrombocytopenia is also common

TREATMENT

The treatment depends on the underlying etiology of microangiopathy

Thank you