Atlas of Pediatric Peripheral Blood Smears

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First Edition
The authors of this Pediatric Hematology atlas hope that the publication of this atlas will help technologists and clinicians in their assessment of the peripheral blood smear of newborns, infants and children. This project has provided us with an exciting and challenging opportunity that we continue to find extremely rewarding. We trust you will benefit from our ongoing fascination with the data produced by these smears.

The critical review of the peripheral blood smear on a newborn provides the perfect opportunity to evaluate a medical condition with a very small amount of blood. Thoughtful interpretation of the smear along with the medical history has proven to be an invaluable tool in evaluating the status of the newborn or child. Frequently, obtaining a blood specimen from the newborn or infant can be a very challenging task. Obtaining a heel stick specimen for a blood smear is a relatively easy procedure and one that can provide solid information.

Pediatric hematological disorders can be complex. The recognition and diagnosis of hereditary and genetic disorders and syndromes such as Fanconi anemia, Diamond Blackfan and hereditary hemolytic anemias can be difficult. The peripheral blood smear is the most helpful adjunct to the history and physical findings in diagnosing these disorders. Some acquired disorders are also unique to neonates or infants. Rh and ABO incompatibility in the newborn, transient erythroblastopenia of childhood (TEC), hemolytic uremic syndrome (HUS) in infants and children are unique examples. All of these have specific findings that can direct the clinician to the correct diagnosis.

Similar challenges are present with white cell disorders. Children that present with unique conditions such as Pelger-Huët anomaly, Chediak Higashi Syndrome or May Hegglin anomaly can be diagnosed by review of the peripheral blood smear.

Most of the hereditary thrombocytopenias (HT) are diagnosed in infancy and childhood. The thrombocytopenia seen in May Hegglin anomaly, Bernard Soulier disease and other giant platelet syndromes can be detected and diagnosed by examination.

Over the past 30 years, the authors have accumulated vast experience, a database of case studies and a library of peripheral blood smears. This atlas has been compiled to help aid future pediatric hematologists and laboratory technologists to skillfully assess the peripheral smear in the diagnosis of malignant and benign hematological disorders.
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1. Erythrocyte Morphology: Normal

**Erythrocyte (Red Cell)**

A normal erythrocyte is a mature non-nucleated red cell appearing as a biconcave disc. It should stain pink to red with a central pallor occupying 1/3 the diameter of the cell with a Wright-Giemsa stain.

**Normal Morphology (Newborn)**

When reviewing the peripheral smear of the newborn, one's perception of "normal" changes dramatically. A normal newborn smear may have a few burr (echinocytes) cells, an occasional nucleated red blood cell, a few targets (coddocytes), a few fragmented RBCs (schistocytes), some spherocytes, and some polychromasia, etc. The important concept is that there is a much wider variation in the type of red cells observed on the peripheral smear of an infant than is seen in the typical adult smear. If these observations were made on an adult blood film, there would be cause for concern; however, on the newborn smear, these findings are considered normal.

Another finding that should be noted is that the typical newborn has a high MCV (mean corpuscular volume), so the red cells are macrocytic. Frequently the hemoglobin is elevated, so the red cells and white cells may appear smudgy and distorted. Making a good peripheral smear is the critical first step in the evaluation of the blood smear.
Normal Morphology (Infants and Children)

Red Blood Cells: Erythrocytes are the most numerous cells encountered in the peripheral smear. Morphologic examination should include assessment of size, shape, color (pallor), and the presence of inclusions. Size: Normal red cells are the size of the lymphocyte nucleus, with a diameter of 7 to 8 microns and a mean corpuscular volume (MCV) from 75 to 90 femtoliters (fL) depending on age. Shape: Red cells should appear round and have a smooth contour. Color: Approximately one third of the red cell should have a central pallor. A decrease in this proportion indicates hyperchromia. Complete loss of central pallor is characteristic of spherocytes. An increase in the amount of pallor indicates hypochromia. Most of the time, hypochromic cells are microcytic and are commonly seen in iron deficiency anemia, thalassemias and chronic disease anemias in childhood.

As the newborn smear is unique, the child’s smear is also unique. Although the red cell findings seen in the newborn disappear, other changes occur that are unique to children. The MCV for children is lower than that seen in adults. Typically, the MCV is from 75 to 80 fL. The lymphocyte count in children is inversely proportionate to the adult reference ranges, with children having higher lymphocyte counts than neutrophil counts. This begins to gradually change toward adult ranges around 12 years of age. A very common finding on the blood smear of children is the presence of reactive lymphocytes. Viral infections are prevalent among both pre-school and elementary school children, and the manifestation of these childhood illnesses is reflected in the number of reactive lymphocytes seen on the peripheral smear.

Figure 7. Normal Morphology (1 year old)
2. Erythrocyte Morphology: Abnormal

**Acanthocytes (Spur Cells)**

Acanthocytes are spheroidal red cells lacking central pallor with thorn-like projections of variable sizes located at irregular intervals.

Acanthocytes are seen in

- Hereditary abetalipoproteinemia
- Hereditary acanthocytosis
- End stage liver disease
- Anorexia nervosa
- Malnutrition
- Post splenectomy
- Intravenous hyperalimentation particularly with intralipid infusion

**Bite Cells**

Bite cells are red cells from which precipitated denatured hemoglobin has been removed by the spleen. The “bite” appears as half a circle removed from the edge of the red blood cell.

Bite cells are commonly seen in

- Glucose 6 phosphate dehydrogenase (G-6-PD) deficiency
- Unstable hemoglobin variants
- Congenital Heinz body anemia (congenital bite cell anemia)

![Figure 8. Acanthocytes (Spur Cells)](image8)

![Figure 9. Acanthocytes](image9)

![Figure 10. Bite Cells](image10)

![Figure 11. Bite Cells](image11)
Blister Cells

Blister cells are erythrocytes in which there is a large vacuole or clear zone on one side of the erythrocytes. Blister cells are commonly seen in
- Glucose 6 phosphate deficiency (G-6-PD)
- Oxidant injury associated hemolytic process
- Sickle cell disease

Echinocytes (Burr Cells, Crenated Cells)

Echinocytes are normochromic red cells with blunt short projections, which are evenly distributed over the surface of the red blood cell. Echinocytes are commonly seen in
- Artifact due to slow drying of the smear because of high humidity
- Renal disease
- Liver disease
- Pyruvate kinase deficiency

Figure 12. Blister Cells

Figure 13. Blister Cells

Figure 14. Echinocytes (Burr Cells)

Figure 15. Burr Cells
**Fragmented Red Cells (Schistocytes, Helmet Cells, Keratocytes)**

Fragmented red cells are red cells that are injured and torn due to a microangiopathic process in which fibrin strands are generated and responsible for injury to the red cells.

Fragmented cells are commonly seen in
- Hemolytic uremic syndrome (HUS)
- Thrombotic thrombocytopenic purpura (TTP)
- Disseminated intravascular coagulation (DIC)
- Other microangiopathic hemolytic anemias

**Macrocytes**

Macrocytes are large red cells with a high mean corpuscular volume (MCV), usually greater than 100 fL. Their hemoglobin concentration is normal. They may be oval or round.

Macrocytes are commonly seen in
- Normal newborn
- Chromosomal disorders (e.g., Trisomy 21)
- Drug associated macrocytosis (e.g., anticonvulsants, antidepressants, sulpha, chemotherapeutic agents, estrogen and antiretroviral agents)
- Folate deficiency
- B₁₂ deficiency
- Dyserythropoiesis
- Myelodysplasia
- Preleukemia
- Hypothyroidism
- Liver disease

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Figure 16. Fragmented Red Cells (Schistocytes, Helmet Cells)

Figure 17. Fragmented Red Cells

Figure 18. Macrocytes

Figure 19. Macrocyte
Microcytes

Microcytes are smaller than normal red cells with a MCV less than 75 fL in children less than 5 years of age and less than 80 fL in children over 5 years of age. Microcytosis is usually associated with hypochromia.

Microcytic hypochromic cells are commonly seen in
- Iron deficiency anemia
- Lead poisoning
- Thalassemias
- Hemoglobin E
- Later stage of chronic disease anemia
- Sideroblastic anemia

Ovalocytes (Elliptocytes)

Ovalocytes and elliptocytes are red cells that are elongated with blunt ends and parallel sides. The term ovalocyte is interchangeable with the term elliptocyte. Their names are descriptive of their appearance.

A small number of elliptocytes are seen in the normal peripheral smear.

Elliptocytes are commonly seen in
- Hereditary elliptocytosis (>25%)
- Renal and liver diseases
- Vitamin B₁₂ deficiency
- Myelodysplasia

Figure 20. Microcytes

Figure 21. Microcyte

Figure 22. Ovalocytes (Elliptocytes)

Figure 23. Ovalocytes
Polychromatophilic Red Cells (Reticulocytes)

A polychromatophilic red cell is a non-nucleated red cell precursor slightly larger than the mature red cell (8-10 microns in diameter). It contains RNA in addition to the hemoglobin and stains gray blue or pale purple with Wright-Giemsa stain. It has a deep blue granular or filamentous structure when supravitally stained.

Reticulocytes are seen in
- Hemolytic anemias
- Blood loss anemias
- Recovering anemia

Figure 24. Polychromatophilic Red Cells

Figure 25. Polychromatophilic Red Cells

Sickle Cells (Drepanocytes)

Sickle cells are red cells with two pointed ends which are in the shape of a crescent or sickle. This is due to the polymerization of deoxygenated hemoglobin S causing changes to the red blood cell making it less deformable and much more rigid.

Sickle cells are usually seen in
- Sickle cell anemia
- Hemoglobin SC
- S beta thalassemia
- Hemoglobin SD

Figure 26. Sickle Cells (Drepanocytes)

Figure 27. Sickle Cells
Spherocytes

Spherocytes are dense, staining spherical red cells with normal or slightly reduced MCV without any central pallor.

Spherocytes are commonly found in
- Hereditary spherocytosis
- ABO incompatibility
- Autoimmune hemolytic anemia (warm antibody type)
- Infections (e.g., EBV, CMV, E. coli, Sepsis/Urosepsis)
- Severe burns
- DIC and HUS
- Post transfusion

Stomatocytes

Stomatocytes are red cells with a central clear opening appearing like a mouth, hence the name stoma, meaning mouth.

Stomatocytes are commonly seen in
- Hereditary Stomatocytosis
- Liver disease
- Obstructive lung disease
- Artifact (most frequent cause of stomatocytes) is caused by the smear drying too slowly in a humid environment
**Target Cells (Codocytes)**

Target cells have a central hemoglobinized area within the surrounding area of pallor. These morphological features give these red cells the appearance of a sombrero or a bull’s eye. Target cells are larger than normal cells with excess cell membrane.

Target cells are commonly seen in:
- Hemoglobin C
- Sickle cell disease
- Hemoglobin E
- Hemoglobin H disease
- Thalassemias
- Iron deficiency anemia
- Liver disease
- Target cells are seen with most of the hemoglobinopathies

**Teardrop Cells (Dacrocytes)**

Red cells in the shape of a teardrop or a pear with a single short or long, blunted or rounded end are called teardrop cells.

Teardrop cells are commonly seen in:
- Osteopetrosis
- Myelofibrosis
- Bone marrow infiltrated with hematological or non-hematological malignancies
- Iron deficiency anemia
- Pernicious anemia
- Anemia of renal disease
- Artifact of slide preparation

![Figure 32. Target Cells (Codocytes)](image1)

![Figure 33. Target Cells](image2)

![Figure 34. Tear Drop Cells (Dacrocytes)](image3)

![Figure 35. Teardrop Cells](image4)
3. Erythrocyte Inclusions

**Basophilic Stippling**

Basophilic stippling is a collection of fine or coarse granules in the red cells. Clinically insignificant, fine stippling is often seen in reticulocytes. Coarse stippling is seen in clinically significant conditions with impaired hemoglobin synthesis and is a result of accumulation of abnormal aggregates of ribosomes and polyribosomes.

Basophilic stippling is commonly seen in:
- Lead poisoning
- Iron deficiency anemia
- Thalassemia
- Refractory anemia
- Congenital hemolytic anemias

**Hemoglobin C Crystals**

Hemoglobin C crystals are dense rhomboid, tetragonal or rod-shaped structures within red cells. They often distort the red cell and project beyond its rim.

Hemoglobin C crystals are commonly seen in:
- Hgb CC
- Hgb SC

(They are readily seen in Hgb CC or Hgb SC status post-splenectomy.)

**Heinz Bodies**

Heinz bodies are multiple blue-purple inclusions attached to the inner surface of the red cell membrane. They are not visible in Wright-Giemsa-stained blood films, but are visible in supravitally stained smears. Heinz bodies are precipitated normal or unstable hemoglobin usually secondary to oxidant stress.

Heinz bodies are commonly seen in:
- G6PD deficiency
- Unstable hemoglobins
- Congenital Heinz body (bite cell) anemias

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**Figure 36. Basophilic Stippling**

**Figure 37. Basophilic Stippling**

**Figure 38. Heinz Bodies**

**Figure 39. Heinz Bodies**

**Figure 40. Hemoglobin C Crystals**
**Hemoglobin H Inclusions**

Hemoglobin H inclusions are precipitated excess beta hemoglobin chains, usually seen with brilliant crystal blue stain, and not visible with Wright-Giemsa stain. These inclusions are small, evenly distributed within red cells producing a golf ball appearance. They are fine, deep staining and numerous, varying from 20 to 50 per red cell. They are seen in Hemoglobin H disease (Alpha Thalassemia — 3 gene deletion).

**Howell-Jolly Bodies**

Howell-Jolly bodies are small round bodies composed of DNA, about 1 µm in diameter, usually single and in the periphery of a red cell. They are readily visible on the Wright-Giemsa-stained smear. The spleen is responsible for the removal of nuclear material in the red cells, so in absence of a functional spleen, nuclear material is removed ineffectively.

Howell-Jolly bodies are seen in
- Post splenectomy
- Functional asplenia
- Anatomical absence of spleen

**Pappenheimer Bodies**

Pappenheimer bodies are small dark inclusions 2 to 5 per red cell appearing either singly or in pairs. They are smaller than Howell-Jolly bodies. They are visible on the Wright-Giemsa-stained smear, also stain positive with the Prussian Blue stain, suggestive of presence of iron.

Pappenheimer bodies are seen in iron overload.
4. Miscellaneous Abnormalities

**Agglutination**

Red cell agglutination occurs when red blood cells clump in irregular masses. Agglutination is secondary to cold agglutinins, most commonly an IgM antibody.

Red cell agglutination is most commonly seen in

- Mycoplasma infections
- Viral infections (e.g., influenza, parainfluenza)
- Lymphoproliferative disorders
- Plasma cell dyscrasias
- Paroxysmal cold hemoglobinuria

![Figure 47. RBC Agglutination](image)

**Rouleaux**

Rouleaux formation is a common artifact in the thick area of any blood film. True Rouleaux is seen in the thin part of the blood smear. There are four or more red cells organized in a linear arrangement like a stack of coins. The central pallor is generally apparent.

True rouleaux formation is due to increased amounts of plasma proteins primarily fibrinogen and globulins.

Rouleaux are commonly seen in

- Infections
- Inflammation
- Monoclonal gammopathies
- Neoplastic diseases
- AIHA warm antibody disease

![Figure 48. Rouleaux](image)
Hereditary Hemolytic Anemias

Membrane Defects

Hereditary Spherocytosis (HS) is the commonest hereditary hemolytic anemia, inherited as an autosomal dominant disorder of varying severity. The hallmark of HS erythrocytes is increased red cell fragility secondary to loss of membrane surface area, which is also responsible for spherocytic red cells. The increased fragility is caused by a quantitative defect in the membrane proteins, ankyrin, spectrin and others.

Hereditary elliptocytosis (HE) is a common and mild anemia due to a structural defect of the erythrocyte membrane protein, spectrin. It is common in individuals of African and Mediterranean descent. Approximately 85% to 90% of patients have only morphological evidence of HE. The remainder of patients have a hemolytic anemia of varying severity. Spherocytic HE and stomatocytic HE (Melanesian or Southeast Asian ovalocytosis) are described. Hereditary Pyropoikilocytosis is a related disorder.

Hereditary pyropoikilocytosis (HPP) is a rare but severe hemolytic anemia in young children, mostly of African descent with a family history of hereditary elliptocytosis (HE). HPP erythrocytes exhibit thermal sensitivity and have a defect in the erythrocyte membrane protein, spectrin. Many patients with HPP proceed to develop mild to moderate HE.

Hereditary stomatocytosis (HSt) is a mild autosomal dominant hemolytic anemia. There is an inherited abnormality in erythrocyte cation permeability, leading to abnormal erythrocyte hydration. The most common defect is in the red cell membrane protein, stomatin.
Hereditary xerocytosis is a rare and mild hemolytic anemia, synonymous with dehydrated HST. The defect is in erythrocyte permeability, with a net loss of potassium and proportionate gain of sodium leading to a decrease in cell water content. A specific defect in the red cell membrane protein is not known.

Hereditary acanthocytosis is an autosomal recessive, mild hemolytic anemia due to a defect in beta lipoprotein (abetalipoproteinemia).

**Enzyme Defects**

Glucose 6 Phosphate Dehydrogenase (G6PD) deficiency is the commonest cause of hemolytic anemia worldwide. It is an X-linked hemolytic anemia of varying severity. It is commonly seen in the people of Southeast Asian, Mediterranean, Middle Eastern and African descent. Some of the population have mild continuous hemolytic process and some have only hemolysis with oxidant stress.

Pyruvate kinase deficiency (PK) is a rare, usually severe hemolytic anemia inherited as autosomal recessive genetic disorder, commonly found in German, Mennonite and Amish populations. It is the commonest enzyme deficiency in the Embden-Meyerhof pathway.

**Congenital Dyserythropoietic Anemia**

Congenital dyserythropoietic anemia (CDA) is a rare hemolytic anemia associated with ineffective erythropoiesis. There are three types of CDA.

Type I: A mild hemolytic process with mild splenomegaly, inherited as autosomal recessive disease

Type II: (HEMPAS) significant hemolysis inherited as autosomal recessive genetic disorder with severe dyserythropoiesis

Type III: An asymptomatic disorder with mild anemia and mild dyserythropoiesis inherited as autosomal dominant disorder
Hemoglobinopathies

Listed below are several common pediatric hemoglobinopathies, for which examination of peripheral blood smears can lead to rapid and accurate diagnosis.

Sickle syndrome includes:

- Homozygous SS disease (Sickle Cell Anemia)
- Hemoglobin SC
- Sickle β° Thalassemia (S β° Thal)
- Sickle β+ Thalassemia (S β+ Thal)
- AS (sickle trait)

Hb C (AC or CC) includes Hb C β° Thalassemia

Hemoglobin E Disease

Thalassemia syndromes will be discussed in the section of microcytic hypochromic anemias.

Sickle hemoglobinopathies are most commonly present in people of African descent. In the United States, these pathologies are seen in African Americans, African immigrants, Caribbean and Central Americans, particularly from the Caribbean coast of Central America. In addition, sickle syndromes are seen in Middle Eastern, Mediterranean and East Indian populations. Hemoglobin S is a qualitative defect of the β globin chain of the hemoglobin in which there is a substitution of amino acid valine for glutamic acid leading to polymerization of hemoglobin in the presence of hypoxemia.
Acquired Hemolytic Anemias

Autoimmune Hemolytic Anemia
Autoimmune hemolytic anemia (AIHA) is an autoimmune disorder associated with warm IgG antibodies producing chronic extravascular hemolytic anemia. AIHA can also be associated with cold reactive IgM antibodies which produces a brisk intravascular hemolytic anemia (cold agglutinin disease).

Microangiopathic Hemolytic Anemias
Hemolytic uremic syndrome (HUS) is a triad of hemolytic anemia, thrombocytopenia and uremia. Verotoxin of E. coli is the commonest causative agent, but it is also seen with viral and other bacterial processes.
Thrombotic thrombocytopenic purpura (TTP) is a rare microangiopathic hemolytic anemia associated with thrombocytopenia. It is rare in children and seen infrequently in teenagers. It is seen mostly in adults.

Disseminated intravascular coagulopathy (DIC) is a symptom of severe systemic bacterial infection in which endotoxin produced by bacteria activates the coagulation cascade, injuring the red cells, causing hemolysis. DIC is also associated with trauma, massive transfusion, sepsis and some neoplastic diseases.

Neonatal Autoimmune Hemolytic Anemia

**ABO Incompatibility**

ABO incompatibility is the commonest alloimmune hemolytic anemia in the newborn demonstrating varying severity. A small percentage will have severe neonatal jaundice and anemia needing exchange transfusion. The majority will have mild to moderate jaundice and anemia.

**Rh Incompatibility**

Rh incompatibility is responsible for hemolysis due to fetal to maternal transfer of Rh positive cells resulting in immunization of the Rh negative mother, in whom Rh antibodies are made, which pass transplacentally to the fetus, causing hemolysis.

Pancytopenias

Classification:
- Bone marrow failure syndromes
- Autoimmune pancytopenia
- Myelodysplastic syndrome (MDS)
- Leukemias

Bone Failure Syndromes

Acquired: Aplastic anemia

Inherited:
- Fanconi anemia (FA)
- Diamond Blackfan anemia (DBA)
- Dyskeratosis congenita
- Reticular dysgenesis
- Shwachman diamond syndrome
- Amegakaryocytic thrombocytopenia (AMT)
- Pre-leukemia (Monosomy 7)

Others:
- Downs
- Dubowitz
- Seckel

Acquired Aplastic Anemia

Acquired aplastic anemia is an uncommon disorder which presents with progressive pancytopenia. Fifty percent of aplastic anemias are due to viral infections, drugs, toxins, exposure to chemicals and systemic diseases with the remaining 50% being idiopathic. Ten percent of idiopathic aplastic anemias recover spontaneously with 10% converting into acute leukemia and the remaining 80% needing treatment.

Fanconi Anemia (FA)

FA is a rare autosomal recessively inherited bone marrow failure syndrome of varying severity. It is associated with multiple congenital anomalies involving the skeletal system, skin, kidneys, heart, lungs, and brain. The defect lies in the repair of DNA. Patients with FA have a very high incidence of cancers and acute leukemias at a young age.

Figure 72. Fanconi Anemia

Diamond Blackfan Anemia (DBA)

DBA is an autosomal recessive disorder associated with skeletal malformation (thumb abnormalities and short stature). Usually, it is a pure red cell anemia, but in 5%-10% of patients, there may be associated thrombocytopenia and/or neutropenia.

Figure 73. Diamond Blackfan Anemia

Dyskeratosis Congenita (DC)

DC is a rare form of ectodermal dysplasia. The diagnostic triad consists of
- Reticular hyperpigmentation of face, neck and shoulders
- Dystrophic nails
- Mucous membrane leukoplakia
Fifty percent of patients with DC develop aplastic anemia in the second decade of life and 10% develop cancer in the third and fourth decades of life.

- Chromosomal syndromes of Downs, other trisomies, monosomy 7
- Refractory anemias

**Seckel Syndrome**

Seckel syndrome is a rare autosomal recessive disorder associated with severe microcephaly, mental retardation, short stature and bird-like facies. Ten percent to 15% of the patients develop progressive and severe aplastic anemia.

**Autoimmune Pancytopenia**

Autoimmune pancytopenias are associated with autoimmune antibodies leading to antibody mediated destruction of cells and is usually associated with hypercellular bone marrow. The common causes are

- Infections (e.g., EBV, CMV, HIV and Parvovirus)
- Collagen vascular disorders particularly in systemic lupus erythematosus (SLE)
- Autoimmune lymphoproliferative syndrome (ALPS)

**Myelodysplastic Syndrome (MDS)**

MDS is usually associated with pancytopenia and normocellular to hypocellular bone marrow. MDS is characterized by megaloblastic and dyserythropoietic erythropoiesis with maturational defect.

Dysmyelopoiesis is common with maturational aberrations in myeloid cells. Megakaryopoiesis often is atypical. The common causes of MDS are

- Drugs, toxins and chemicals
- Radiation
- Preleukemia

**Down Syndrome**

Down syndrome (Trisomy 21) is often associated with episodes of dysmyelopoiesis.

Leukemoid reaction: With stress, severe leukocytosis, mostly neutrophilia with some increase in bands and metamyelocytes

Transient myeloproliferative disorder (TMD): Transiently there is significant leukocytosis with increases in mature and immature myeloid cells, including blasts

Acute leukemias

Severe aplastic anemia

MDS with cytopenias leading to preleukemia/leukemia
Microcytic Anemias

Iron Deficiency Anemia

Iron Deficiency Anemia (IDA) is the most common anemia worldwide and commonly affects infants between the ages of 9 months and 2 years, because of poor iron intake. Chronic blood loss is the commonest cause of IDA in children over 2 years of age.

Lead Poisoning

Anemia of lead intoxication is largely caused by inhibition of heme synthesis and inhibition of pyramidal 5’ nucleosidase. Anemia of lead poisoning mimics IDA but has a normal iron profile. Basophilic stippling in the red blood cells and polychromatophilic cells are the hallmarks of lead poisoning.

Thalassemias

Alpha thalassemia is a genetic disorder in which α globin synthesis is decreased giving imbalance to the hemo-globin leading to ineffective erythropoiesis and microcytic hypochromic red cells.

- α thalassemia 2 gene deletion (trait)
- α thalassemia 3 gene deletion (Hg “H” disease)
- α thalassemia major (4 gene deletion, incompatible with life)
- α thalassemia 3 gene deletion (Hgb “H” disease) and Hb Constant Spring
Beta thalassemia is a genetic disorder with decreased production of β chains leading to imbalance in hemoglobin with ineffective erythropoiesis producing microcytic, hypochromic erythrocytes.

- β thalassemia trait
- β thalassemia major

Hemoglobin E is a frequent variant in SE Asia. Hemoglobin E trait (Hb AE) patients are healthy but have microcytosis and target cells in the peripheral blood smear. Homozygous Hb E (EE) patients have anemia with microcytosis, MCV 65-67 fl. Hb E β thalassemia resembles β thalassemia major.

Other combinations of β thalassemias include

- S β⁰ Thalassemia
- S β⁺ Thalassemia
- E β⁰ Thalassemia
- E β⁺ Thalassemia
- C β⁰ Thalassemia
- C β⁺ Thalassemia

**Normocytic Anemias**

*Acquired pure red cell anemia.* Transient erythroblastopenia of childhood (TEC) is an autoimmune red cell aplasia usually associated with a preceding viral infection. It affects children between the ages of 1 month and 5 years, and is a transient condition.

Anemias associated with neoplastic disorders include

- Chronic disease anemia
- Acquired marrow failure syndrome
- Aplastic anemia

Figure 82. β Thalassemia trait

Figure 83. β Thalassemia major

Figure 84. Hb E β Thalassemia

Figure 85. Transient Erythroblastopenia of Childhood
Macrocytic Anemias
Folate deficiency
Vitamin B₁₂ deficiency

Myelodysplastic syndrome (MDS) is a rare disorder, often associated with a chromosomal aberration and is frequently a pre-leukemic condition.

Summary
Ninety-five percent of pediatric anemias are diagnosed by the morphology of the peripheral smear. These include
- HS: spherocytes and polychromasia
- HE: elliptocytes and ± polychromasia
- HPP: pyropoikilocytes and polychromasia
- Pyknocytosis: pyknocytes
- G6PD Deficiency: blister cells, bite cells, spherocytes and polychromasia
- Pyruvate kinase deficiency: polychromasia, burr/fragments
- AIHA: (IgG antibodies) spherocytes, rouleaux and polychromasia
- Cold antibody disease (IgM/complement): agglutination
- HUS: helmet cells, spherocytes, polychromasia and thrombocytopenia
- TTP: fragments, polychromasia and thrombocytopenia
- Sickle cell anemia: sickle forms and target cells, polychromasia, H-J bodies, pappenheimer bodies
- SC hemoglobinopathy: target cells, ovalocytes and holly leaf cells
- SBº thalassemia: microcytic, hypochromic cells and target cells
- Hgb C hetero/homozygous: target cells
- Iron deficiency anemia: microcytic hypochromic red cells and anisocytosis
- Lead poisoning: basophilic stippled red cells
- Beta thalassemia major (Cooley’s anemia): very microcytic hypochromic cells with anisocytosis, nucleated red cells present
- Beta thalassemia trait: microcytic hypochromic red cells
- Alpha thalassemia trait/Hgb H disease: microcytic hypochromic red cells with polychromasia and anisocytosis
White Blood Cells (Leukocytes)

- Myeloid/monocytic cells
- Lymphocytes

Myelopoiesis

In bone marrow a hematopoietic stem cell commits to form progenitor myeloid and monocytic cells which eventually leads to the formation of neutrophils, eosinophils, basophils and monocytes.

Neutrophil, Segmented (Segs)

The segmented neutrophil is the predominant white blood cell in the peripheral blood. It is 10 µm to 15 µm in diameter with pale pink cytoplasm and specific fine granules. Rare azurophilic (primary granules) are seen. The nucleus is lobulated (between 2 and 5 lobes) and the lobes are connected by a thin filament.

Band Neutrophil

Band neutrophils constitute from 0% to 5% of the nucleated cells under normal conditions in the peripheral blood. The band is round to oval in shape and 10 µm to 18 µm in diameter. The nucleus can be band-like, sausage-shaped, S-, C- or U-shaped and may be twisted and folded on itself. The cytoplasm is pale with specific granules in it. Increased numbers of bands appear in the blood in a number of physiologic and pathologic states.

Bands are increased in the peripheral blood in the following conditions:

- Severe infections
  - Sepsis/bacteremia
- Inflammation
- Stress
**Basophil**

In the normal physiological state there are very few (0%-1%) basophils in the peripheral blood. All basophils, from the basophilic myelocyte to the mature segmented basophil, are characterized by the presence of a moderate number of large coarse and densely stained granules of varying sizes and shapes. The granules in the Wright–Giemsa-stained preparation are blue-black; some may be purple to red.

Basophils are increased in the blood in

- Myeloproliferative disorders (e.g., chronic myelogenous leukemia)
- Hypersensitivity reactions
- Mastocytosis
- Xeroderma pigmentosa
- Hypothyroidism

**Eosinophil**

Eosinophils are distinct cells, about the size of a neutrophil (10 µm -15 µm) with abundant cytoplasm filled with many large, coarse, orange-red granules which are refractile because of their crystalline structure. About 80% of segmented eosinophils will have the classic two-lobe appearance. Only 1% to 8% of circulating leukocytes are eosinophils.

Morphologically abnormal eosinophils are seen in

- Myelodysplastic syndrome
- Megaloblastic anemias

Eosinophils are increased in the following conditions:

- Allergies
- Parasitic infestations
- Infections
- Acute leukemia
- Myeloproliferative diseases
- Hypereosinophilic syndrome
- Drug-associated
Monocytes

Monocytes are larger cells, 12 µm to 20 µm in diameter. The majority of monocytes are round with smooth edges. Usually, there is abundant gray to gray-blue cytoplasm which may contain fine, evenly distributed granules and vacuoles. The nucleus is usually indented, the chromatin is condensed and occasionally a small and inconspicuous nucleolus is seen. Monocytes are seen in 1% to 5% of the leukocytes in the peripheral smear.

Monocytes are increased in the following conditions:

- Chronic infection (e.g., tuberculosis)
- Recovery from severe neutropenia in neoplastic or aplastic disorders
- Benign neutropenia

Lymphocytes

Most lymphocytes seen on a blood smear are fairly homogeneous. Lymphocytes are small, round- to ovoid-shaped cells that range in size from 7 µm to 15 µm with round to oval nuclei. Some normal lymphocytes are medium-sized due to an increase in the amount of cytoplasm. The nucleus appears dense or coarse and clumped with ridges of chromatin and parachromatin. Nucleoli, if present, are small and inconspicuous. The majority of lymphocytes have a scant amount of pale blue to basophilic agranular cytoplasm.
**Lymphocytes, Large Granular**  
(Atypical Lymphocytes)

These atypical-appearing lymphocytes are large with abundant cytoplasm-containing areas having azurophilic granules. The nucleus has clumped chromatin and no visible nucleoli. These cells are either suppressor/cytotoxic T lymphocytes or natural killer cells.

Large granular lymphocytes are commonly found with viral infections.

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**Reactive Lymphocytes**

Reactive lymphocytes are notable due to their remarkable heterogeneity. They tend to be large with abundant cytoplasm. They are indented by surrounding red cells, and they may have blue skirting (blue outline around the cytoplasm). Another descriptive term used is the “fried egg” appearance. This cell corresponds to the Downey Type II cell. Accompanying this type of reactive lymphocyte, plasmacytoid lymphocytes are frequently seen. These lymphocytes have deeply basophilic cytoplasm and resemble plasma cells. Their size varies from small to moderate and may have one or more prominent nucleoli. They correspond to Downey Type III cells. The Downey Type I cell which is not observed as frequently is small with a sightly basophilic cytoplasm and an indented or lobulated nucleus.

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Reactive lymphocytes are frequently seen in children with viral diseases, but the condition where reactive lymphocytes demonstrating all the Downey type cells are seen is usually infectious mononucleosis.

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**Infectious Mononucleosis**

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8. White Blood Cell Morphology: Abnormal

Neutrophil Abnormalities: Toxic Changes

**Toxic Granulation**
The presence of large purple to dark blue cytoplasmic granules in neutrophils (altered primary granules)

Döhle Bodies
Single or multiple, pale blue, spindle-shaped inclusions located on the rim of the cytoplasm of neutrophils

Toxic changes are seen in:
- Infection
- Thermal injury
- Trauma

Döhle bodies are seen in acute infections and May-Hegglin anomaly.

**Hypersegmented Neutrophils**
Large hypersegmented neutrophils are a result of megaloblastic hematopoiesis. In megaloblastic myelopoiesis, eosinophils and basophils are large and also hypersegmented. To be considered hypersegmented, neutrophils should have 6 or more lobes.

Megaloblastic hematopoiesis is seen in
- Vitamin B₁₂ deficiency
- Folate deficiency
- Effects of chemotherapeutic agents (e.g., 6-Mercaptopurine or methotrexate)
**Pelger-Huët Cell Anomaly**

Neutrophils with bi-lobed nuclei in the “pince-nez” or dumbbell conformation (two round lobes connected by a distinct thin filament) are designated as Pelger-Huët cells. They occur as an inherited autosomal dominant abnormality of nuclear segmentation referred to as Pelger-Huët anomaly.

Non-inherited Pelger-Huët cells are called pseudo Pelger-Huët cells and are seen in:
- Myelodysplastic syndromes
- Myeloid malignancies
- Drugs (e.g., sulfonamides, colchicine)
- HIV infection

The nucleus may show abnormal lobulation. Dysplastic neutrophils may be pseudo Pelger-Huët cells. They may have:
- Auer rods
- A decrease or absence of primary and secondary granules
- Functional defects

**Auer Rods**

Auer rods are pink or red, rod-shaped cytoplasmic inclusions seen in myeloid cells and occasionally in monocytes. Auer rods are thought to be an abnormal crystalline form of primary granules.

- Acute myeloid leukemia
- Myelodysplastic/pre-leukemic states

An immature myeloid cell containing multiple Auer rods clumped together is known as a faggot cell, and is seen in acute promyelocytic leukemia.

**Dysplastic Neutrophils**

Dysplastic neutrophils are characteristic of myelodysplastic syndromes. Morphologically, there is dysynchronous maturation of nucleus and cytoplasm. In the cytoplasm, the primary and secondary granules are often decreased or absent making the cytoplasm appear pale and bluish.
Normal Platelets (Thrombocytes)

Platelets are small non-nucleated cells derived from the cytoplasmic fragments of megakaryocytes and are variable in size. Normal-sized platelets are 1.5 µm to 3 µm in diameter and have fine purple-red granules aggregated at the center or dispersed throughout the cytoplasm.

- Normal platelets are 1.5 µm to 3 µm in diameter
- Large platelets are 4 µm to 7 µm in diameter
- Giant platelets are greater than 7 µm in diameter and may be 10 µm to 20 µm.
- Small (micro) platelets are less than 1.5 µm in diameter

Large Platelets

Large platelets are usually 4 µm to 7 µm in diameter. Large platelets are commonly seen in:

- Reactive thrombocytosis
- Autoimmune thrombocytopenia
- Myeloproliferative disorder/leukemoid reaction
- Myelodysplastic disorder
- Neoplastic diseases: Acute Megakaryocytic Leukemia (M7)
- Hereditary thrombocytopenias
**Giant Platelets**

Giant platelets are larger than 7 µm and may be 10 µm to 20 µm in diameter. The periphery of the giant platelet may be round or scalloped. The cytoplasm may contain fine azurophilic granules or the granules may fuse into giant forms. Giant platelets are commonly seen in

- Myelodysplastic disorder
- Hereditary Thrombocytopenias, such as:
  - May-Hegglin anomaly (giant platelets and Döhle bodies in the neutrophils)
  - Bernard Soulier syndrome
  - Alport syndrome
  - Storage pool syndrome

**Small Platelets (Microthrombocytes)**

Microplatelets are usually less than 1.5 µm in diameter and are not counted adequately by the impedance blood cell counters, giving spuriously low platelet counts. Microplatelets are seen in Wiskott Aldridge Syndrome (WAS).

**Hypogranular Platelets (Dysplastic Platelets)**

Hypogranular platelets have very few purple-red granules compared to normal platelets. The cells may be normal in size, shape and configuration or they may be enlarged and misshaped. The cytoplasm stains pale blue or blue gray. Hypogranular platelets are commonly seen in

- EDTA-induced artifact
- Myeloproliferative disorder
- Myelodysplastic disorder
- Grey platelet syndrome
**Platelet Satellitism**
Platelets sometimes clump and adhere to neutrophils and more rarely to monocytes forming “platelet rosettes,” which is known as *platelet satellitism*. Platelet satellitism is a cause of spurious thrombocytopenia because the cellular aggregates are counted as leukocytes rather than platelets.

![Figure 124. Platelet Satellitism](image1)

**Thrombocytosis**
Causes may include
- Reactive thrombocytosis
  - Post infection
  - Inflammation
  - Chronic diseases
  - Juvenile rheumatoid arthritis (JRA)
  - Collagen vascular diseases
  - Benign tumors: adenomas, lipomas
  - Ganglioneuroblastoma/neuroblastoma
- Essential thrombocythemia

![Figure 125. Thrombocytosis](image2)

**Quantitative Disorders of Platelets**
- Thrombocytopenia
- Thrombocytosis

**Common Causes of Thrombocytopenia**
- Decreased production
  - Aplastic anemia
  - Acute leukemia
  - Viral infections
    * Parvovirus
    * CMV
  - Amegakaryocytic thrombocytopenia (AMT)
- Increased destruction
  - Immune thrombocytopenia
    * Idiopathic thrombocytopenic purpura (ITP)
    * Neonatal alloimmune thrombocytopenia (NAITP)
  - Disseminated intravascular coagulation (DIC)
  - Hypersplenism
Leukemias and Myeloproliferative Diseases

Acute lymphoblastic leukemia (ALL) is the single most common form of pediatric cancer accounting for 25% of all childhood cancer. The incidence of ALL in the United States is one in every 29,000 children per year. The overall cure rate for children is 85% with long-term, disease-free survival.

Acute leukemia results from uncontrolled proliferation of immature cells; its cause is unknown but genetic and environmental factors play a role.

Chronic leukemias are rare and chronic myelogenous leukemia accounts for less than 5% of leukemias. Chronic lymphocytic leukemia does not occur in children.

Classification of acute leukemias:
- Acute lymphoblastic leukemia (ALL)
- Acute myeloid leukemia (AML)

FAB classification – AML
- M0: AML, minimally differentiated
- M1: Acute myeloblastic leukemia, without maturation
- M2: Acute myeloblastic leukemia with maturation
- M3: Acute promyelocytic leukemia
- M4: Acute myelomonocytic leukemia
- M4eo: Acute myelomonocytic leukemia with bone marrow eosinophilia
- M5a: Acute monoblastic leukemia, or M5b, acute monocytic leukemia
- M6: Erythroleukemia
- M7: Acute megakaryoblastic leukemia

WHO classification of leukemias include:
- Morphology of leukemic cells
- Genetic alterations
- Immunophenotypic data
- Biological and clinical features

The FAB classification of leukemias is built on the morphology of the leukemic cells and their unique cytochemical-staining characteristics. The World Health Organization (WHO) classification is based on flow cytometry, cytogenetic, and molecular findings. The WHO classification has much greater clinical and prognostic relevance.

Lymphoblastic Leukemia

L1 Lymphoblastic Leukemia
These cells are relatively small (1 ½ times a normal lymphocyte) with coarse chromatin and scanty cytoplasm. The chromatin is evenly dispersed and nucleoli are usually not visible. The cells are characterized by a uniform cell population.

L2 Lymphoblastic Leukemia
These cells are characterized by cellular heterogeneity. They are larger than L1 cells with more cytoplasm and prominent nucleoli. They are sometimes difficult to distinguish from a myeloblast.
L3 Lymphoblastic Leukemia

These cells are characterized by the basophilia and prominence of vacuoles in their cytoplasm. They are usually homogeneous in population, about twice the size of a normal lymphocyte with prominent nucleoli.

Myeloid Leukemia

M0 Myeloblastic Leukemia

This cell is large with an absence of granules in the cytoplasm and may or may not have a prominent nucleoli. Differentiation is done by flow cytometry and/or electron microscopy.

M1 Myeloblastic Leukemia

This cell has agranular cytoplasm with maturing cells, promyelocytes onward or monocytes less than 10%. Cytochemical stains and flow cytometry are necessary in their identification. Auer rods may be present.

M2 Myeloblastic Leukemia

This cell has undergone some maturation and may be accompanied by more mature myelocytic cells. Cytoplasmic granules are frequent, and Auer rods may be present.
M3 Promyelocytic Leukemia
There are 2 types of M3 promyelocytes, 1 with cytoplasm densely packed with both blue and pink (nonspecific and specific) granules. There may also be faggots, or slender, elongated Auer rods present. This cell is of the hypergranular variety. The second one has a bi-lobed nucleus (monocytic in appearance) with a paucity of granules.

M4 Myelomonocytic Leukemia
There are 2 types of cells associated with this leukemia. The first is the myeloblast, similar to the M2 described above and the second is the presence of immature monocytes.

M5 Monoblastic Leukemia
This cell is larger than other myeloid cells with a nucleus that has smooth chromatin and very basophilic cytoplasm. There is also a more mature monoblast (M5b) with cells that are more mature and resemble the monocyte seen in the peripheral smear.
M6 Erythroblastic Leukemia
There should be both myeloblasts (like the previous M2) and erythroblasts present. In the peripheral blood, there may be abnormal nucleated red blood cells accompanied by myeloblasts.

Figure 142. M6 Erythroblast

Figure 143. M6 Erythroblast

M7 Megakaryoblastic Leukemia
These cells are undifferentiated with a smooth nucleus, scanty cytoplasm and usually without a nucleoli. They may have cytoplasmic blebbing which helps distinguish these cells.

The use of flow cytometry, cytochemical stains, cytogenetics and molecular diagnostics is essential in making an accurate diagnosis.

Figure 144. M7 Megakaryoblast

Figure 145. M7 Megakaryoblast
Myeloproliferative Disorders

Myeloproliferative disorders are rare in pediatrics and are characterized by ineffective hematopoiesis resulting in increases of peripheral blood counts with immature forms.

Types may include

- Chronic myelogenous leukemia (CML)
- Juvenile myelomonocytic leukemia (JMML)
- Transient myeloproliferative disease (TMD)

**Chronic Myelogenous Leukemia (CML)**

CML is rare and the only chronic leukemia that occurs in children, affecting preadolescents, adolescents and young adults. It is associated with the Philadelphia chromosome (Ph+), which is a 9;22 translocation. Usually it is diagnosed incidentally, but the common presentation is splenomegaly with marked leukocytosis.

![Figure 146. Chronic Myelogenous Leukemia](image1.png)

**Juvenile Myelomonocytic Leukemia (JMML)**

JMML is a rare disorder affecting children less than 2 years of age. Clinically they present with skin rash, marked lymphoadenopathy, moderate hepatosplenomegaly and bleeding. It is associated with moderate leukocytosis, monocytosis and thrombocytopenia.

![Figure 147. Juvenile Myelomonocytic Leukemia](image2.png)

**Transient Myeloproliferative Disease (TMD)**

TMD is usually seen in children with Down Syndrome (trisomy 21 or mosaic trisomy 21). It is characterized by uncontrolled proliferation of blasts, usually of megakaryocytic origin. TMD is generally a transient process (70% of patients), but in 30% of the patients develops into M7 (megakaryocytic leukemia).

![Figure 148. Transient Myeloproliferative Disease](image3.png)
11. Miscellaneous

**Infections**

*Infectious Mononucleosis*

Infectious mononucleosis (IM) is a viral infection caused by the Epstein-Barr virus (EBV). IM usually affects adolescents and young adults but in developing countries it affects very young children. Clinical features are fever, pharyngitis, cervical adenopathy and splenomegaly. Laboratory findings of IM include lymphocytosis with atypical lymphocytes, elevated hepatic transaminases and frequent thrombocytopenia.

![Infectious Mononucleosis](image1)

*Figure 149. Infectious Mononucleosis*

*Malaria*

Malaria is a protozoan disease in humans caused by *Plasmodium vivax*, *P. falciparum*, *P. malariae* and *P. ovale*. Malaria is transmitted to humans by the bite of an infected female anopheles mosquito. The clinical features consist of recurring paroxysmal fevers and chills with nausea, headache and extreme malaise. The diagnosis of malaria is made by examination of Wright–Giemsa-stained peripheral blood smears. Thick smears are better for the diagnosis of malaria.

![Malaria](image2)

*Figure 150. Malaria P. Falciparum Gametocyte*

**Borrelia**

Borrelia is a tick- or louse-borne spirochetal infection transmitted by infected deer, rodents or people. The clinical features include cycles of fever with malaise and headaches. Careful examination of Wright–Giemsa-stained peripheral blood smears usually makes the diagnosis. Corkscrew-like spirochetes are seen on the smear.

![Borrelia](image3)

*Figure 151. Borrelia*

**Filaria**

Filariae are transmitted by insect bites (usually mosquitoes); they reside in the lymphatic system, subcutaneous tissue or within body cavities. The microfilariae make their way to the bloodstream and vary in size from 160-315 micrometers in length and 3 µm to 10 µm in width.

![Filaria](image4)

*Figure 152. Filaria*
**Candida Albicans**

Candida albicans (fungi) infection in immunocompromised children can be seen on the peripheral smear.

![Figure 153. Fungus](image)

**Bacteria**

Bacteria, including Staphylococcus aureus, Streptococcus, Meningococcus and Pneumococcal infections can be diagnosed on examination of the peripheral blood smear, especially in immunocompromised or splenectomized children.

![Figure 154. Bacteria](image)

**Chédiak-Higashi Syndrome**

Chédiak-Higashi syndrome is a rare autosomal recessive disorder associated with partial oculo-cutaneous albinism and impaired neutrophil function, leading to increased susceptibility to bacterial infection. This disorder is characterized by the presence of large lysosomal granules in granulocytes, lymphocytes and monocytes in the blood. These large abnormal granules are formed by progressive fusion of azurophilic and specific granules during maturation.

Similar large lysosomal granules have been seen in melanocytes, renal tubular cells, fibroblasts, vascular epithelium, neurons in the central nervous system and ocular cells. In addition to susceptibility to bacterial infection, the patients with Chédiak-Higashi syndrome may develop an accelerated phase with fever, adenopathy, hepatosplenomegaly, pancytopenia and lymphohistiocytic infiltrates in various organs.

![Figure 155. Chédiak-Higashi Syndrome](image)

![Figure 156. Chédiak-Higashi Syndrome](image)
Mucopolysaccharidosis is a group of inherited diseases with specific enzyme deficiencies leading to excessive accumulation of mucopolysaccharides in body tissue. In the peripheral blood there are large, fused azurophilic granules called Alder-Reilly bodies in neutrophils, eosinophils, basophils and infrequently in lymphocytes and monocytes.

Glycogen storage diseases usually affect bone marrow macrophages where there is accumulation of specific by-products of glycogen metabolism (e.g., Niemann-Pick disease, Gaucher disease). Occasionally Niemann-Pick type A and C may have granules in lymphocytes.

Lipid Storage Diseases (Lipidosis). Some storage diseases have prominent azurophilic granules and vacuoles in the lymphocytes, neutrophils, eosinophils and basophils (e.g., in fucosidosis, sialidosis, infantile gangliosidosis, mannosidosis and mucolipidosis types II and III).
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Microscopic Photos = Bold
Subject Headings and Disease States = Italicized
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