Approach to the child with anemia

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INTRODUCTION

The approach to anemia in the pediatric patient is reviewed here. Included are pertinent issues related to the history, physical examination, and initial laboratory work-up; methods for classifying anemia; and algorithms designed to help guide diagnosis.

A systematic approach to the examination of the peripheral blood smear and bone marrow is discussed separately. (See "Evaluation of the peripheral blood smear" and "Evaluation of bone marrow aspirate smears".)

DEFINITION OF ANEMIA

Anemia is defined as reduced blood hemoglobin (HGB) concentration or red blood cell (RBC) mass:

- Hemoglobin (HGB) – A measure of the RBC pigment HGB concentration, expressed as grams per 100 mL (dL) of whole blood. The reference range for HGB in children ages 6 to 12 years old is approximately 11.2 to 14.5 g/dL (112 to 145 g/L).
- Hematocrit (HCT) – The fractional volume of whole blood occupied by RBCs, expressed as a percentage. The reference range for HCT in children ages 6 to 12 years old is 35 to 44 percent.

Reference ranges for HGB and HCT vary with age and sex (table 1). The threshold for defining anemia is HGB or HCT at or below the 2.5th percentile for age and sex based upon reference data from healthy individuals. Previous reports have described lower values for

HGB in Black Americans compared with White Americans (approximately 0.5 to 1 g/dL lower for Black Americans) [1,2]. However, those differences likely reflect health disparities related to social determinants of health. We recommend using the same HGB and HCT thresholds for evaluating anemia in all racial and ethnic groups (ie, we do not assume that a slightly lower value in a Black individual is "normal").

PATIENT CHARACTERISTICS

Causes of anemia in children vary based upon age at presentation, sex, and ethnicity.

Age of patient — The age of the patient is important to consider because reference values of hemoglobin (HGB) and hematocrit (HCT) vary with age and because different causes of anemia present at different ages (table 1):

- **Birth to three months** – The most common cause of anemia in young infants is "physiologic anemia," which occurs at approximately six to nine weeks of age. Erythropoiesis decreases dramatically after birth as a result of increased tissue oxygenation, which reduces erythropoietin production [3,4]. In healthy term infants, HGB levels are high (>14 g/dL) at birth and then rapidly decline, reaching a nadir of approximately 10 to 11 g/dL at six to nine weeks of age, which is called "physiologic anemia of infancy" (also called the "physiologic nadir") (figure 1) [5,6].

  Pathologic anemia in newborns and young infants is distinguished from physiologic anemia by any of the following [3]:

  - Anemia (HGB <13.5 g/dL) within the first month of life
  - Anemia with lower HGB level than is typically seen with physiologic anemia (ie, <9 g/dL)
  - Signs of hemolysis (eg, jaundice, scleral icterus, or dark urine) or symptoms of anemia (eg, irritability or poor feeding)

  Common causes of pathologic anemia in newborns include blood loss, immune hemolytic disease (ie, Rh or ABO incompatibility), congenital infection, twin-twin transfusion, and congenital hemolytic anemia (eg, hereditary spherocytosis, glucose-6-phosphate dehydrogenase [G6PD] deficiency) (algorithm 1).

  Hyperbilirubinemia in the newborn period suggests a hemolytic etiology; microcytosis at birth suggests chronic intrauterine blood loss or thalassemia.

  Compared with term infants, preterm infants are born with lower HCT and HGB, have shorter red blood cell (RBC) life span, and have impaired erythropoietin production due to immature liver function [3]. Hence, the decline in RBC production occurs earlier after

birth and is more severe than the anemia seen in term infants. This is referred to as "anemia of prematurity" and is discussed in detail separately. (See "Anemia of prematurity (AOP)".)

- **Infants three to six months** – Anemia detected at three to six months of age suggests a hemoglobinopathy. Nutritional iron deficiency is an unlikely cause of anemia before the age of six months in term infants. (See "Diagnosis of sickle cell disorders" and "Diagnosis of thalassemia (adults and children)".)

- **Toddlers, children, and adolescents** – In toddlers, older children, and adolescents, acquired causes of anemia are more likely, particularly iron deficiency anemia. Screening for iron deficiency anemia is recommended in all children at 9 to 12 months of age. At that age, children who are exclusively breastfed or breastfed without sufficient iron supplementation are at highest risk for iron deficiency. In contrast, infants who primarily receive iron-fortified formula during the first year of life are at risk for iron deficiency after transition to cow milk. Therefore, additional laboratory screening should be considered in children with additional risk factors (eg, excessive cow milk intake in toddlers 12 to 36 months of age, onset of menarche in adolescent females). Recommendations for screening for iron deficiency are discussed in detail separately. (See "Iron deficiency in infants and children <12 years: Screening, prevention, clinical manifestations, and diagnosis", section on 'Screening recommendations'.)

Sex — Some inherited causes of anemia are X-linked (eg, G6PD deficiency and X-linked sideroblastic anemia) and occur most commonly in males. In postmenarchal girls, excessive menstrual bleeding is an important cause of anemia, and clinicians should suspect and evaluate for an underlying bleeding disorder. (See "Diagnosis and management of glucose-6-phosphate dehydrogenase (G6PD) deficiency", section on 'Epidemiology' and "Abnormal uterine bleeding in adolescents: Evaluation and approach to diagnosis", section on 'Causes of heavy menstrual bleeding' and "Causes and pathophysiology of the sideroblastic anemias", section on 'X-linked sideroblastic anemia (ALAS2 mutation)'.)

Ethnicity — Ethnic background can be helpful in guiding the work-up for hemoglobinopathies and enzymopathies (eg, G6PD deficiency). As examples:

- HGB S and C are most commonly seen in individuals of African or Hispanic descent, and Middle Eastern populations. (See "Diagnosis of sickle cell disorders" and "Hemoglobinopathy: Screening and counseling in the reproductive setting and fetal diagnosis", section on 'Epidemiology of carrier state and disease'.)

- Thalassemia syndromes are more common in individuals of Mediterranean and Southeast Asian descent. (See "Diagnosis of thalassemia (adults and children)", section

on 'Epidemiology'.)

- G6PD deficiency is more common among Sephardic Jewish individuals; Black individuals from sub-Saharan Africa or Brazil; African Americans; and people from Thailand, Sardinia, Greece, South China, and India (areas where malaria was once endemic) (figure 2). (See "Diagnosis and management of glucose-6-phosphate dehydrogenase (G6PD) deficiency", section on 'Epidemiology'.)

EVALUATION

History — The evaluation of a child with anemia begins with a thorough history. The degree of symptoms, past medical history, family history, dietary history, and developmental history may provide important clues to the cause of anemia (table 2):

- **Symptoms** – Characterizing the symptoms helps elucidate the severity and chronicity of anemia and may identify patients with blood loss or hemolytic etiologies:

  - **Symptoms attributable to anemia** – Common symptoms of anemia include lethargy, tachycardia, and pallor. Infants may present with irritability and poor oral intake. However, because of the body's compensatory abilities, patients with chronic anemia may have few or no symptoms compared with those with acute anemia at comparable hemoglobin (HGB) levels.

  - **Symptoms of hemolysis** – Changes in urine color, scleral icterus, or jaundice may indicate the presence of a hemolytic disorder. Hemolytic episodes that occur only in male family members may indicate the presence of a sex-linked disorder, such as glucose-6-phosphate dehydrogenase (G6PD) deficiency. (See "Overview of hemolytic anemias in children" and "Diagnosis and management of glucose-6-phosphate dehydrogenase (G6PD) deficiency", section on 'Clinical manifestations'.)

  - **Bleeding symptoms** – Specific questions related to bleeding from the gastrointestinal tract, including changes in stool color, identification of blood in stools, and history of bowel symptoms, should be reviewed. It is also important to determine whether there is a personal or family history of inflammatory bowel disease, celiac disease, intestinal polyps, colorectal cancer, hereditary hemorrhagic telangiectasia, von Willebrand disease, platelet disorders, or hemophilia. (See "Lower gastrointestinal bleeding in children: Causes and diagnostic approach" and "Approach to the child with bleeding symptoms".)

    Severe or recurrent epistaxis also may result in anemia from blood loss and iron deficiency. (See "Evaluation of epistaxis in children".)

In adolescent girls, menstrual history should be obtained, including duration and amount of bleeding. Severe epistaxis and/or heavy menstrual bleeding should raise suspicion for an underlying bleeding disorder [7]. (See "Abnormal uterine bleeding in adolescents: Evaluation and approach to diagnosis", section on 'History'.)

- **Pica** – The presence of pica, the intense craving for nonfood items, should be assessed given its strong association with iron deficiency. In young children, pica may manifest as craving dirt, rocks, and paper. In adolescents, craving for ice, or pagophagia, may be more common.

- **Past medical history** – The past medical history should focus on characterizing past episodes of anemia and identifying underlying medical conditions:

  - **Birth history** – The birth and neonatal history should include gestational age, duration of birth hospitalization, and history of jaundice (including onset and need for phototherapy) and/or anemia in the newborn period. Results of newborn screening (which typically includes screening for sickle cell disease) should be reviewed. (See "Alloimmune hemolytic disease of the newborn: Postnatal diagnosis and management" and "Anemia of prematurity (AOP)" and "Diagnosis of sickle cell disorders", section on 'Newborn screening' and "Diagnosis and management of glucose-6-phosphate dehydrogenase (G6PD) deficiency", section on 'Neonatal jaundice'.)

  - **History of anemia** – Previous complete blood counts (CBCs) should be reviewed, and, if prior anemic episodes occurred, they should be characterized (including duration, etiology, therapy, and resolution). Prior episodes of anemia suggest an inherited disorder, whereas anemia in a patient with previously documented normal CBC suggests an acquired etiology. Patients with certain hemoglobinopathies (such as HGB E or the various thalassemias) may have a history of treatment on multiple occasions for an erroneous diagnosis of iron deficiency anemia. (See "Diagnosis of thalassemia (adults and children)".)

  - **Underlying medical conditions** – Past medical history and review of symptoms should be obtained to elucidate chronic underlying infectious or inflammatory conditions that may result in anemia. Travel to/from areas of endemic infection (eg, malaria, hepatitis, tuberculosis) should be noted (the Centers for Disease Control and Prevention provides updated information on malaria and tuberculosis). Recent illnesses should be reviewed to investigate for possible infectious etiologies of anemia.

- **Drug and toxin exposure** – Current and past medications (including homeopathic or herbal supplements) should be reviewed with particular attention to oxidant drugs that

can cause hemolysis, particularly in patients with underlying G6PD deficiency (eg, drugs such as fluoroquinolones, dapsone, nitrofurantoin, and sulfonylureas; foods such as fava beans; and others, as summarized in the table (table 3)). Possible environmental toxin exposure should be explored, including lead exposure and nitrates in well water. (See "Diagnosis and management of glucose-6-phosphate dehydrogenase (G6PD) deficiency", section on 'Inciting drugs, chemicals, foods, illnesses' and "Childhood lead poisoning: Exposure and prevention".)

- **Family history** – Family history of anemia should be reviewed in depth. Family members with jaundice, gallstones, or splenomegaly should be identified. Asking if family members have undergone cholecystectomy or splenectomy may aid in the identification of additional individuals with inherited hemolytic anemias. (See "Overview of hemolytic anemias in children", section on 'Intrinsic hemolytic anemias'.)

- **Dietary history** – The dietary history is focused on assessing iron intake and, to a lesser degree, folate and vitamin B12 content.

  For infants and toddlers, the type of diet, type of formula (if iron fortified), and age of infant at the time of discontinuation of formula or breast milk should be documented. In addition, the amount and type of milk the patient is drinking should be determined. Infants and children who are exclusively fed goat milk can develop anemia due to folate deficiency [8-10]. Exclusively breastfed infants who do not receive sufficient iron supplementation may be anemic at the time of the initial screening at age 9 to 12 months, whereas infants receiving iron-fortified formula until age 12 months are unlikely to be anemic at this time, though they may be at risk for iron deficiency during the second year of life after transitioning to cow's milk. Pica (particularly pagophagia, the eating of ice) may suggest lead poisoning and/or iron deficiency. (See "Iron deficiency in infants and children <12 years: Screening, prevention, clinical manifestations, and diagnosis" and "Causes and pathophysiology of vitamin B12 and folate deficiencies" and "Childhood lead poisoning: Clinical manifestations and diagnosis".)

  In older children and adolescents, it is important to ask about special dietary practices (eg, vegetarian or vegan diet), junk food intake, and picky eating habits. Additional details of dietary screening for iron deficiency are provided separately. (See "Iron requirements and iron deficiency in adolescents".)

- **Developmental history** – Parents/caregivers should be asked questions to determine if the child has reached age-appropriate developmental milestones. Developmental delay can be associated with iron deficiency, lead toxicity, vitamin B12/folic acid deficiency, and Fanconi anemia [11]. (See "Developmental-behavioral surveillance and screening in primary care", section on 'Approach to surveillance'.)

Physical examination — The physical examination also may provide important clues to the cause of anemia. Particular focus should be directed to examination of the skin, eyes, mouth, facies, chest, hands, and abdomen (table 4).

Pallor is assessed by examining sites where capillary beds are visible (eg, conjunctiva, palm, and nail beds). However, the sensitivity of clinical assessment of pallor in these locations in detecting severe anemia (ie, HGB <7 g/dL) is only approximately 50 to 60 percent [12-14].

Patients with hemolytic processes resulting in anemia may present with signs of scleral icterus, jaundice, and hepatosplenomegaly resulting from increased red cell destruction. However, as with the clinical detection of anemia through evaluation of pallor, clinical detection of jaundice often is poor. As an example, in an emergency department setting, the clinical detection of jaundice was found to have sensitivity and specificity of only approximately 70 percent [15].

Laboratory evaluation — Initial laboratory studies include a CBC with red blood cell (RBC) indices and review of the peripheral blood smear. A reticulocyte count should be obtained, although this is not necessary for the diagnosis of iron deficiency anemia in children <2 years old who present with a mild microcytic anemia and a suggestive dietary history. (See "Iron deficiency in infants and children <12 years: Screening, prevention, clinical manifestations, and diagnosis", section on 'Evaluation for suspected iron deficiency anemia'.)

The CBC, RBC indices, blood smear, and reticulocyte count are used to focus the diagnostic considerations and guide further testing to confirm the etiology of anemia (algorithm 2 and algorithm 3). (See 'Diagnostic approach' below.)

Complete blood count — The CBC provides information about the RBCs and other cell lines (ie, white blood cells [WBCs] and platelets). All three cell lines should be evaluated for abnormalities.

Hemoglobin and hematocrit — Reference ranges for HGB and hematocrit (HCT) vary with age, so it is important to use age- and sex-adjusted ranges (figure 1 and table 1).

Falsely elevated results may be obtained when HGB and HCT values are measured using capillary samples (eg, finger or heel "sticks"), particularly when using microhematocrit measurements, although the likelihood of masking significant anemia is low [16-18]. Spurious results may also occur with automated counters in the presence of lipemia, hemolysis, leukocytosis (with WBC counts >50 × 10^9/L), or high immunoglobulin levels [1].

Red blood cell indices — The RBC indices are an integral part of the evaluation of the anemic child. These include:

- **Mean corpuscular volume (MCV)** – MCV is measured directly by automated blood cell counters and represents the mean value (in femtoliters [fL]) of the volume of individual

RBCs in the blood sample. Reference values for MCV vary based upon age (infants have increased MCV compared with older children) (table 1). A useful rule of thumb to remember approximate age-appropriate lower reference limits for MCV values is 70 + age in years.

MCV is the most useful RBC parameter when evaluating a patient with anemia and is used to classify the anemia as microcytic (ie, ≤2.5th percentile), normocytic, or macrocytic (ie, ≥97.5th percentile), as discussed below. (See 'Microcytic anemia' below and 'Normocytic anemia' below and 'Macrocytic anemia' below.)

Because reticulocytes have a greater MCV than do mature cells (picture 1), patients with significant degrees of reticulocytosis may have elevated MCV values in the face of otherwise normocytic RBCs [19]. (See 'Macrocytic anemia' below and "Macrocytosis/Macrocytic anemia".)

- **Red cell distribution width (RDW)** – The RDW is a quantitative measure of the variability of RBC sizes in the sample (anisocytosis). Reference values vary little with age and are generally between 12 and 14 percent [16].

- **Mean corpuscular hemoglobin concentration (MCHC)** – The MCHC is a calculated index (MCHC = HGB/HCT) yielding a value of grams of HGB per 100 mL of RBC. MCHC values vary depending upon the age (infants have higher values than older children) and sex (males have slightly higher values than females) of the child. MCHC also increases with decreasing gestational age [20]. MCHC measurements may vary slightly based upon the technology used and should be interpreted using the reference range for the specific laboratory.

  The MCHC provides a quantitative assessment of the degree of hypo- or hyperchromia (MCHC ≤32 and ≥35 g/dL, respectively). Hypochromia and hyperchromia usually can be appreciated on the peripheral smear (picture 2 and picture 3) [21].

White blood count and platelet count — The other cell lines may provide clues to the underlying cause of anemia (algorithm 3). Leukocytosis (high total WBC count) most commonly suggests an infectious etiology or, less commonly, an acute leukemia. Hypersegmented neutrophils suggest vitamin B12 deficiency. Thrombocytosis (high platelet count) is a common finding in iron deficiency [22], and it also frequently occurs as part of the acute phase reaction in response to infection and other inflammatory conditions, particularly Kawasaki disease. (See "Approach to the patient with neutrophilia" and "Kawasaki disease: Clinical features and diagnosis".)

Leukopenia, neutropenia, and/or thrombocytopenia may signify abnormal bone marrow function or increased peripheral destruction of blood cells:

- Causes of bone marrow suppression/failure include transient suppression due to viral infection, drugs or toxins, nutritional deficiency (eg, folic acid or vitamin B12 deficiency and, rarely, iron deficiency), acute leukemia, or aplastic anemia.

- Increased peripheral destruction of blood cells may be due to splenic hyperfunction ("hypersplenism"), microangiopathic hemolytic anemia (eg, hemolytic uremic syndrome), or an autoimmune process (eg, systemic lupus erythematosus, Evans syndrome, autoimmune lymphoproliferative disease)

Reticulocyte count — Reticulocytes are the youngest red cells in the circulation and are identified by the presence of residual RNA (picture 1 and picture 4). When interpreting the reticulocyte count, attention must be paid to the particular reticulocyte parameter reported (percentage versus absolute count). It is often helpful to estimate the corrected reticulocyte count (ie, the reticulocyte count corrected for the degree of anemia).

- **Reticulocyte percentage** – The reticulocyte is reported as a percentage of the RBC population. After the first few months of life, the reference reticulocyte percentage is the same as that of the adult: approximately 1.5 percent [3].

- **Absolute reticulocyte count (ARC)** – The ARC is the product of the total RBC count multiplied by the reticulocyte count percentage:

  ARC = Percent reticulocytes × RBC count/L

  The ARC is calculated and reported by many automated cell counters. ARC is expected to increase in the presence of anemia, although laboratories do not provide reference ranges adjusted for the level of anemia. In a patient with anemia, ARC values within the reference range (<100 × 10^9/L) generally indicate an inappropriately low erythropoietic response [23].

- **Corrected reticulocyte count** – Estimating the corrected reticulocyte count can be a useful method to determine whether the bone marrow response to anemia is appropriate. The calculation is based on the measured reticulocyte count, measured hematocrit, and normal hematocrit for the patient's age and sex (normal values for hematocrit are summarized in the table (table 1)):

  Corrected reticulocyte count = Measured reticulocyte count [percent] × (measured hematocrit ÷ normal hematocrit for age)

  A corrected reticulocyte count <2 percent is inappropriately low in the setting of anemia.

- **Interpretation** – The reticulocyte count is an indication of bone marrow erythropoietic activity and is used to classify the bone marrow response to anemia (see 'Reticulocyte response' below):

- Anemia with a high reticulocyte count reflects an increased erythropoietic response to hemolysis or blood loss
- Anemia with a low or normal reticulocyte count reflects deficient production of RBCs

Blood smear — A review of the peripheral smear is an essential part of any anemia evaluation. Even if the patient's RBC indices are within reference range, review of the blood smear may reveal abnormal cells that can help identify the cause of anemia. (See "Evaluation of the peripheral blood smear".)

The following features should be noted:

- **RBC size** – A normal RBC should have the same diameter as the nucleus of a small lymphocyte (picture 5). This comparison will help the investigator identify the patient with microcytosis (picture 2) or macrocytosis (picture 6).

- **Central pallor** – The normal mature RBC is a biconcave disc (picture 7). As a result, RBCs on the peripheral smear demonstrate an area of central pallor, which, in normochromic RBCs, is approximately one-third of the diameter of the cell (picture 5). Increased central pallor indicates hypochromic cells, which most often are seen in iron deficiency (picture 2) and thalassemia (picture 8). On the other hand, spherocytes (picture 3) and reticulocytes (picture 1) do not display central pallor, because they are not biconcave discs.

- **Fragmented cells** – Although the patient's overall RBC indices may be within reference range, review of the blood smear may reveal the presence of small numbers of fragmented cells, indicating a microangiopathic process(picture 9). (See "Overview of hemolytic anemias in children" and "Non-immune (Coombs-negative) hemolytic anemias in adults", section on 'Fragmentation'.)

- **Other features** – Other anemias may be characterized by typical morphologic abnormalities, which may go undetected without inspection of the peripheral smear; these include:

  - Sickle cells, as seen in sickle cell disease (picture 10) (see "Diagnosis of sickle cell disorders")

  - Spherocytes (picture 3), as seen in hereditary spherocytosis and acute hemolysis, or elliptocytes, as seen in congenital elliptocytosis (picture 11) (see "Hereditary spherocytosis" and "Hereditary elliptocytosis and related disorders")

  - Stomatocytes, as seen in hereditary or acquired stomatocytosis (picture 12) (see "Hereditary stomatocytosis (HSt) and hereditary xerocytosis (HX)")

- Pencil poikilocytes, which can be seen in iron deficiency anemia or thalassemia (picture 2)
- Target cells, as seen in the various hemoglobinopathies, including thalassemia, as well as in liver disease and post-splenectomy (picture 13 and picture 8) (see "Burr cells, acanthocytes, and target cells: Disorders of red blood cell membrane")
- Bite cells and Heinz bodies (picture 14) are seen in hemolytic anemia due to oxidant sensitivity, such as G6PD deficiency (see "Diagnosis and management of glucose-6-phosphate dehydrogenase (G6PD) deficiency")
- The presence of numerous nucleated RBCs indicates rapid bone marrow turnover and is seen with hemolytic processes (picture 10 and picture 15)
- RBC agglutination (picture 16) is seen in cold agglutinin hemolytic anemia (see "Autoimmune hemolytic anemia (AIHA) in children: Classification, clinical features, and diagnosis", section on 'Cold AIHA')
- Howell-Jolly bodies (picture 17) are associated with absence or hypofunction of the spleen (see "Splenomegaly and other splenic disorders in adults", section on 'Asplenia or hyposplenia')
- Basophilic stippling (picture 18) is classically seen in lead poisoning and may also be present in thalassemia, sickle cell anemia, and sideroblastic anemia (see "Childhood lead poisoning: Clinical manifestations and diagnosis")

The appearance of the patient's leukocytes should also be noted:

- Increases in circulating neutrophils, especially increased numbers of band forms or toxic changes (picture 19), or the presence of atypical lymphocytes (picture 20) suggest the possibility of infectious or inflammatory conditions (see "Approach to the patient with neutrophilia" and "Approach to the child with lymphocytosis or lymphocytopenia")
- Hypersegmented neutrophils (picture 21) suggest vitamin B12 or folate deficiency
- The presence of early WBC forms (eg, blasts) (picture 22) along with anemia should raise the suspicion of leukemia or lymphoma (see "Overview of the clinical presentation and diagnosis of acute lymphoblastic leukemia/lymphoma in children")

DIAGNOSTIC APPROACH

The history, physical examination, and initial laboratory tests are used to narrow the diagnostic possibilities and guide further testing.

Abnormalities in other cell lines — The first step in narrowing the diagnostic possibilities is determining whether the patient has isolated anemia or if other cell lines (ie, white blood cells [WBCs] and platelets) are also abnormal (algorithm 3):

- **Pancytopenia** – Causes of pancytopenia in children include infection, myelosuppressive medications, leukemia, aplastic anemia, and hypersplenism. (See "Aplastic anemia: Pathogenesis, clinical manifestations, and diagnosis" and "Overview of the clinical presentation and diagnosis of acute lymphoblastic leukemia/lymphoma in children" and "Approach to the child with an enlarged spleen".)

- **Anemia with thrombocytopenia** – Causes of anemia associated with low platelet count include hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, and Evans syndrome. Rarely, children with severe iron deficiency anemia may also have thrombocytopenia. (See "Overview of hemolytic uremic syndrome in children" and "Pathophysiology of TTP and other primary thrombotic microangiopathies (TMAs)" and "Warm autoimmune hemolytic anemia (AIHA) in adults", section on 'Evans syndrome'.)

- **Anemia with thrombocytosis** – Iron deficiency anemia is commonly associated with thrombocytosis but can also be associated with thrombocytopenia [22]. Other causes of anemia associated with elevated platelet count include post-splenectomy anemia and infection or inflammation. (See "Iron deficiency in infants and children <12 years: Screening, prevention, clinical manifestations, and diagnosis" and "Approach to the patient with thrombocytosis".)

- **Anemia with leukocytosis** – Causes of anemia associated with elevated WBC count include leukemia and infection. (See "Overview of the clinical presentation and diagnosis of acute lymphoblastic leukemia/lymphoma in children".)

Classification of anemia — Anemias are classified based upon red blood cell (RBC) size (ie, mean corpuscular volume [MCV]) and the physiologic response of the bone marrow (ie, the reticulocyte response). Approaching the evaluation of an anemic patient using these classification schemes helps to further narrow the diagnostic possibilities (algorithm 2).

Microcytic anemia — Microcytic anemia (picture 2) is defined as anemia with a low MCV (ie, ≤2.5th percentile for age and sex) (table 1). (See 'Red blood cell indices' above.)

The most common causes of microcytic anemia in children are iron deficiency and thalassemia (algorithm 2) [1,24].

The red cell distribution width (RDW) can be helpful in differentiating iron deficiency from thalassemia. Anisocytosis (high RDW) is typical of iron deficiency, whereas the RDW is usually within reference range in patients with thalassemia (though elevated RDW can occur). (See

"Iron deficiency in infants and children <12 years: Screening, prevention, clinical manifestations, and diagnosis" and "Diagnosis of thalassemia (adults and children)".)

Normocytic anemia — Normocytic anemia is defined as anemia with an MCV within reference range (ie, between the 2.5th and 97.5th percentile for age and sex (table 1)). (See 'Red blood cell indices' above.)

Common causes of normocytic anemia include hemolytic anemias, blood loss, infection, medication, and anemia of chronic disease. Other causes of normocytic anemia include hypothyroidism and chronic kidney disease. Transient erythroblastopenia of childhood is an acquired red cell aplasia that typically presents with a progressive normocytic anemia in otherwise healthy children and is a diagnosis of exclusion. (See "Overview of hemolytic anemias in children" and "Anemia of chronic disease/anemia of inflammation" and "Overview of causes of anemia in children due to decreased red blood cell production", section on 'Transient erythroblastopenia of childhood'.)

Macrocytic anemia — Macrocytic anemia (picture 6) is defined as anemia with a high MCV (ie, ≥97.5th percentile for age and sex (table 1)). (See 'Red blood cell indices' above.)

The most common cause of macrocytosis in children is exposure to certain medications (eg, anticonvulsants, zidovudine, and immunosuppressive agents) [24,25]. Other causes include vitamin B12 or folate deficiency, liver disease, Diamond-Blackfan anemia, hypothyroidism, and aplastic anemia (algorithm 2). Isolated macrocytosis is also commonly seen in children with Down syndrome [26].

Reticulocyte response — The reticulocyte count is especially helpful in evaluating children with normocytic anemia (algorithm 2 and algorithm 3) (see 'Reticulocyte count' above):

- **High reticulocyte count** – A high reticulocyte count (>3 percent) reflects an increased erythropoietic response to blood loss or hemolysis (table 5). Common causes include hemorrhage, autoimmune hemolytic anemia, membranopathies (eg, hereditary spherocytosis), enzymopathies (eg, glucose-6-phosphate dehydrogenase [G6PD] deficiency), hemoglobinopathies (eg, sickle cell disease), and microangiopathic hemolytic anemia (eg, hemolytic uremic syndrome) (algorithm 2 and algorithm 3). (See "Overview of hemolytic anemias in children".)

- **Low or normal reticulocyte count** – A low or normal reticulocyte count reflects deficient production of RBCs (ie, a reduced marrow response to the anemia).

  Causes of inadequate marrow response include infections, lead poisoning, hypoplastic anemias, transient erythroblastopenia of childhood (TEC), Diamond-Blackfan anemia (which typically presents with macrocytic anemia), drugs (most drugs that decrease erythropoiesis affect other cell lines as well; cisplatin is an example of a medication that

can cause isolated suppression of erythropoiesis), and kidney disease (algorithm 2 and algorithm 3). (See "Overview of causes of anemia in children due to decreased red blood cell production".)

These two categories are not mutually exclusive, however. Hemolysis can be associated with a low reticulocyte count if there is a concurrent disorder that impairs RBC production (eg, infection). Similarly, anemia due to acute blood loss can be associated with low reticulocyte count if there has not been time for the bone marrow to mount an appropriate reticulocyte response, which typically takes approximately one week.

In some cases, the reticulocyte count depends on the phase of the illness. As an example, the reticulocyte count is low in a child during the acute phase of TEC or transient bone marrow suppression caused by a viral illness. However, during the recovery phase from these disorders, children may have elevated reticulocyte counts as the bone marrow recovers and responds to the anemia. The absence of scleral icterus, jaundice, and hepatosplenomegaly distinguishes this recovery process from a hemolytic process. (See "Overview of causes of anemia in children due to decreased red blood cell production", section on 'Transient erythroblastopenia of childhood'.)

Confirmatory testing — Once the diagnostic possibilities have been narrowed based upon the MCV and reticulocyte count, confirmatory testing is performed (algorithm 2 and algorithm 3).

If hemolytic anemia is suspected, testing should include direct antiglobulin test, serum indirect bilirubin, lactate dehydrogenase, and haptoglobin levels. Testing for specific etiologies may include direct antiglobulin test, G6PD deficiency screening test, osmotic fragility, and/or hemoglobin (HGB) analysis/electrophoresis. The diagnostic approach is discussed separately. (See "Overview of hemolytic anemias in children", section on 'Diagnostic approach'.)

If iron deficiency is suspected, additional studies may include iron parameters (eg, serum ferritin). Iron studies are not necessary in children <2 years old who present with a mild microcytic anemia and a suggestive dietary history. A therapeutic trial of iron may be used to confirm the diagnosis in these children. (See "Iron deficiency in infants and children <12 years: Screening, prevention, clinical manifestations, and diagnosis", section on 'Empiric trial of iron therapy'.)

Testing for other nutritional deficiencies and/or lead poisoning may include serum folate, vitamin B12, and lead levels. (See "Clinical manifestations and diagnosis of vitamin B12 and folate deficiency" and "Childhood lead poisoning: Clinical manifestations and diagnosis".)

Bone marrow aspirate and/or biopsy may be necessary to evaluate for leukemia or other diseases of bone marrow failure (eg, aplastic anemia, Diamond-Blackfan anemia).

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Pediatric iron deficiency".)

SUMMARY AND RECOMMENDATIONS

- **Definition of anemia** – The threshold for defining anemia is a hemoglobin (HGB) or hematocrit (HCT) that is ≤2.5th percentile for age and sex (table 1). HGB levels are high (>14 g/dL) at birth and then rapidly decline, reaching a nadir of approximately 10 to 11 g/dL at six to nine weeks of age, which is called "physiologic anemia of infancy" (figure 1). (See 'Definition of anemia' above.)

- **Common causes by age** – The causes of anemia vary based upon the age at presentation (see 'Age of patient' above):

  - In neonates and young infants, alloimmune hemolytic disease, infection, and hereditary disorders are most common (algorithm 1). (See "Alloimmune hemolytic disease of the newborn: Postnatal diagnosis and management" and "Overview of hemolytic anemias in children", section on 'Intrinsic hemolytic anemias'.)

  - In older children, acquired causes of anemia are more likely, particularly iron deficiency anemia (dietary or due to blood loss). (See "Iron deficiency in infants and children <12 years: Screening, prevention, clinical manifestations, and diagnosis".)

- **History and physical examination**

  - Key historical factors in the assessment of a child with anemia include the severity and onset of symptoms, evidence of jaundice or blood loss (gastrointestinal symptoms and menstrual history), drug and toxin exposure, chronic disease, and family history of anemias or hemoglobinopathy (table 2). (See 'History' above.)

  - The physical examination should include a careful assessment for pallor, scleral icterus, jaundice, hepatomegaly, and splenomegaly (table 4). (See 'Physical examination' above.)

- **Laboratory evaluation**

  - The laboratory evaluation begins with a complete blood count (CBC), including red blood cell (RBC) indices, reticulocyte count, and review of the peripheral blood smear. (See 'Laboratory evaluation' above.)

- Examination of the peripheral blood smear may reveal features that suggest a specific cause of anemia and helps to evaluate the possibility of a hematologic malignancy. (See 'Blood smear' above.)

- Once the diagnostic possibilities have been narrowed based upon RBC indices and reticulocyte response, further confirmatory testing is performed, as summarized in the algorithms and discussed above (algorithm 2 and algorithm 3). (See 'Confirmatory testing' above.)

- **Classification by red cell volume** – The mean corpuscular volume (MCV) provides a preliminary categorization of the anemia, which guides additional testing (algorithm 2 and algorithm 3).

  - Common causes of microcytic (ie, low MCV) anemia include iron deficiency and thalassemia

  - Common causes of normocytic (ie, MCV within reference range) anemia include hemolytic anemias, blood loss, infection, medication, and anemia of chronic disease

  - Common causes of macrocytic (ie, high MCV) anemia include medications (eg, antiseizure medications) and deficiency of vitamin B12 or folate (see 'Classification of anemia' above)

- **Reticulocyte response** – The reticulocyte count distinguishes disorders resulting from rapid destruction or loss of RBCs (hemolysis or bleeding) from disorders resulting in an inability to adequately produce RBCs (ie, bone marrow depression). Hemolysis and bleeding are usually associated with a high reticulocyte count (>3 percent), whereas bone marrow depression is associated with a low reticulocyte count (algorithm 2). (See 'Reticulocyte count' above.)

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Topic 5927 Version 39.0

GRAPHICS

Normal values for hematologic parameters in children

Age	Hemoglobin (g/dL)		Hematocrit (%)		MCV (fL)		RDW (%)	
	Lower limit	Upper limit	Lower limit	Upper limit	Lower limit	Upper limit	Lower limit	Upper limit
6 months to <2 years*	11.0¶	13.5	31	42	73	85	12.3	15.6
2 to 6 years	11.0¶	13.7	34	44	75	86	12.0	14.6
6 to 12 years	11.2	14.5	35	44	78	90	11.9	13.8
12 to <18 years								
Female	11.4	14.7	36	46	80	96	11.9	14.6
Male	12.4	16.4	40	51	80	96	11.9	13.7

This table summarizes lower and upper limits (defined as the 2.5th and 97.5th percentile, respectively) for hematologic parameters in children according to age and sex, based upon normative data from healthy populations in the United States. Previous reports have described lower values for hemoglobin in Black Americans compared with White Americans (approximately 0.5 to 1 g/dL lower for Black Americans). However, those differences likely reflect health disparities related to social determinants of health. We recommend using the same hemoglobin and hematocrit thresholds for evaluating anemia in all racial and ethnic groups (ie, we do not assume that a slightly lower value in a Black individual is normal). Reference ranges may differ slightly from one laboratory to another. For more specific guidance, clinicians should refer to the reference ranges at the laboratory performing the testing.

MCV: mean corpuscular volume; RDW: red cell distribution width.

* Normal values for hemoglobin, hematocrit, and MCV change dramatically during the first 6 months after birth. Refer to UpToDate topic on the approach to the child with anemia for a discussion of normal values in young infants.

¶ The lower limit of normal (ie, 2.5th percentile) for hemoglobin at these ages is slightly less than 11 g/dL. However, for the purposes of screening for iron deficiency anemia in infants and young children, many experts use a cutoff of hemoglobin <11 g/dL to define an abnormal screen.

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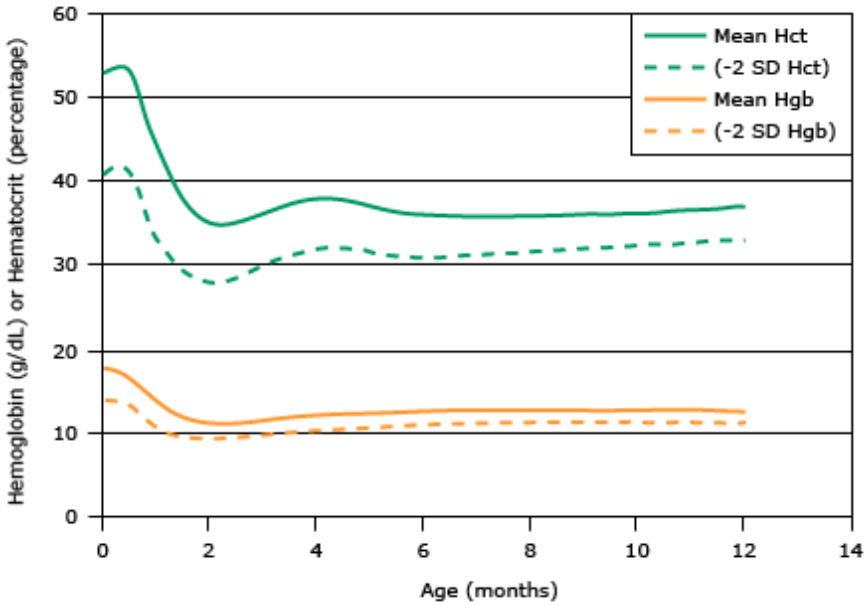
Graphic 101544 Version 11.0

Normal values for hematocrit and hemoglobin during the first year of life in healthy term infants



Hct: hematocrit; SD: standard deviation; Hgb: hemoglobin.

Data from:

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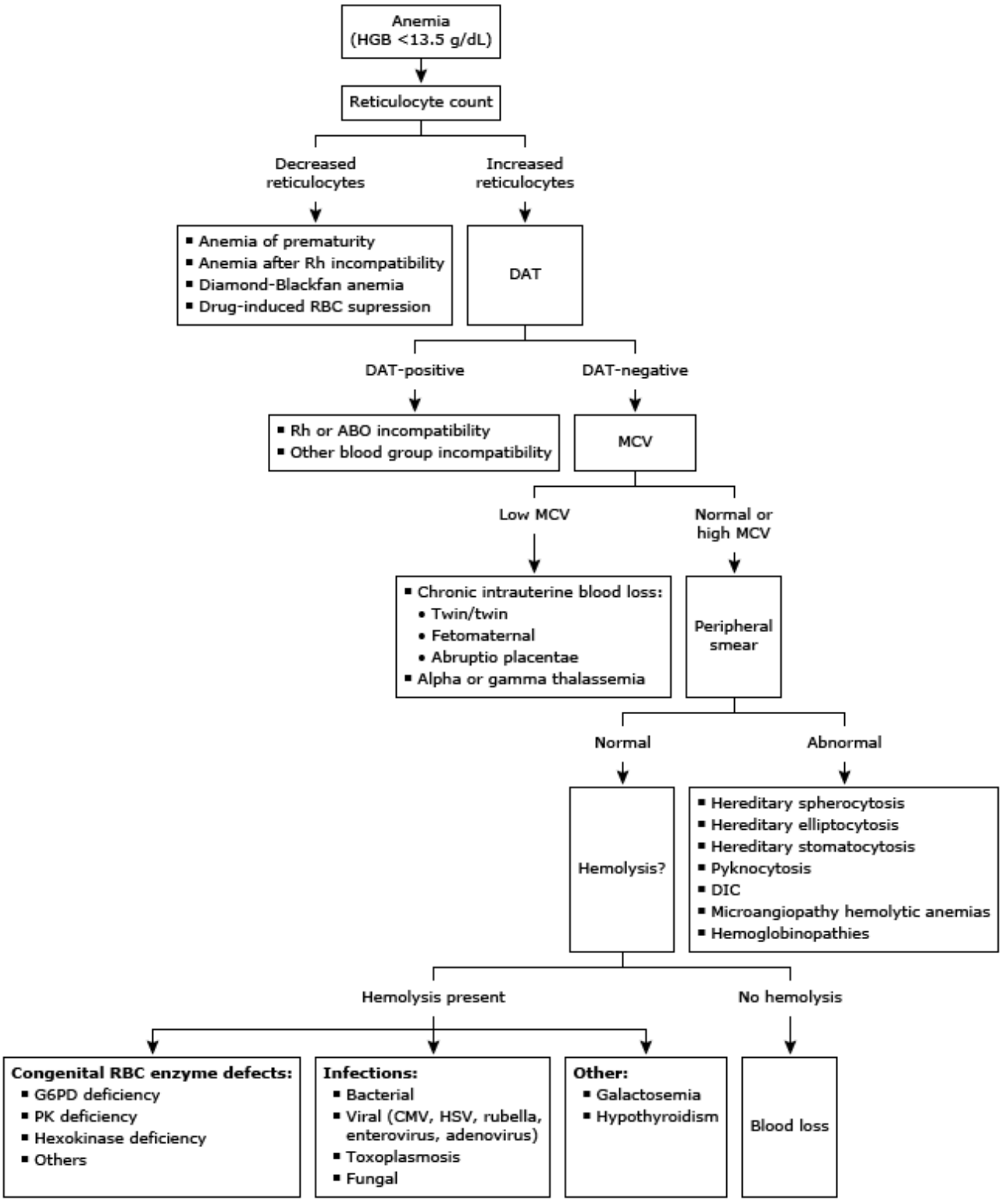
Graphic 81464 Version 3.0

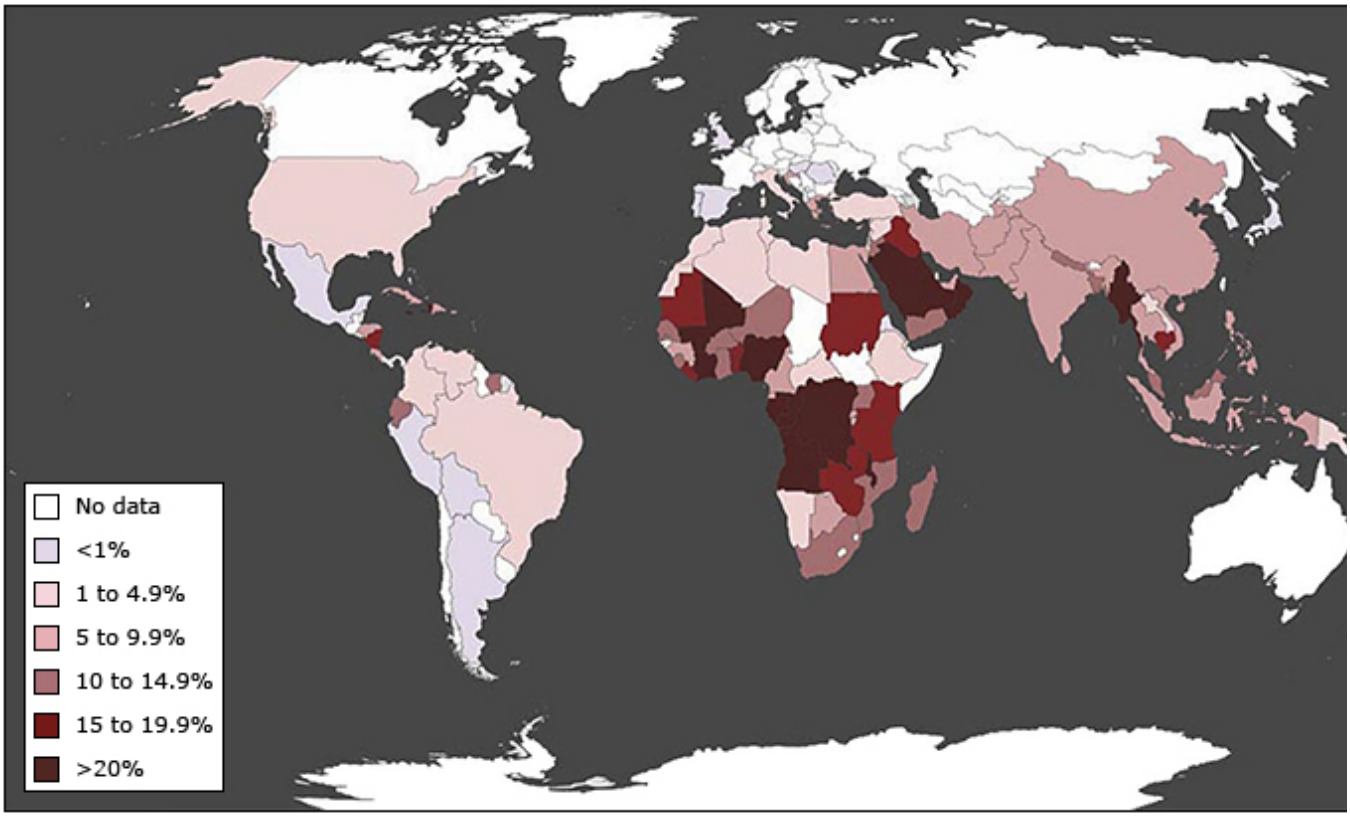
Diagnostic approach to anemia in the newborn



HGB: hemoglobin; RBC: red blood cell; DAT: direct antiglobulin test; MCV: mean corpuscular volume; DIC: disseminated intravascular coagulation; G6PD: glucose-6-phosphate dehydrogenase; PK: pyruvate kinase; CMV: cytomegalovirus; HSV: herpes simplex virus.

Graphic 101423 Version 3.0

Map showing the prevalence of G6PD deficiency throughout the world



The map shows the prevalence of G6PD deficiency variants throughout the world, with darker colors indi higher prevalences. It was constructed from several sources; see the source document for details. Refer t UpToDate for additional information on the epidemiology, clinical presentation, and diagnostic evaluatio G6PD deficiency.

G6PD: glucose-6-phosphate dehydrogenase deficiency.

Graphic 129472 Version 1.0

The medical history in the child with anemia: Elements associated with specific causes of childhood anemia

Patient characteristics
Age: ▪ In neonates and young infants, immune hemolytic disease, infection, and hereditary disorders are most common ▪ Anemia detected at 3 to 6 months of age suggests a hemoglobinopathy ▪ Nutritional iron deficiency is an unlikely cause of anemia before the age of 6 months in term infants ▪ In older children, acquired causes of anemia are more likely, particularly iron deficiency anemia (dietary or due to blood loss)
Sex: ▪ Some inherited causes of anemia are X-linked (eg, G6PD deficiency and X-linked sideroblastic anemia) and occur most commonly in males
Ethnicity/ancestry: ▪ Hemoglobin S and C are most commonly seen in individuals of African or Hispanic descent and Middle Eastern populations ▪ Thalassemia syndromes are more common in individuals of Mediterranean and Southeast Asian descent ▪ G6PD deficiency is more common among Sephardic Jewish individuals; Black individuals from sub-Saharan Africa or Brazil; African Americans; and people from Thailand, Sardinia, Greece, South China, and India
Symptoms
▪ Changes in urine color, scleral icterus, or jaundice suggest a hemolytic disorder ▪ Bloody stools, hematemesis, severe epistaxis, or severe menstrual bleeding suggest anemia from blood loss and/or iron deficiency ▪ Infectious symptoms (eg, fevers, cough) suggest an infectious etiology of anemia
History of anemia
▪ Prior episodes of anemia suggest an inherited disorder ▪ Anemia in a patient with previously documented normal CBC suggests an acquired etiology ▪ Hyperbilirubinemia in the newborn period suggests a hemolytic etiology; microcytosis at birth suggests chronic intrauterine blood loss or thalassemia
Underlying medical conditions
▪ Underlying renal disease, malignancy, or inflammatory/autoimmune disorders may be associated with anemia
Drugs and toxin exposure
▪ Anemia following exposure to oxidant drugs or fava beans suggests G6PD deficiency

- Exposure to paint, home renovations, or use of imported or glazed ceramics suggest lead toxicity

Family history

- Family members with jaundice, gallstones, or splenomegaly suggests an inherited hemolytic anemia

Dietary history

In infants and young children, iron deficiency is suggested by the following:

- Use of low iron formula
- Introduction of unmodified cow's milk before the age of 1 year
- Excessive milk intake (>24 ounces per day)
- Poor intake of iron-rich foods (meats or fortified infant cereal)

Travel history

- Travel to/from areas of endemic infection suggests infectious etiology such as malaria or tuberculosis

Developmental history

- Developmental delay is associated with iron deficiency, vitamin B12/folic acid deficiency, and Fanconi anemia

G6PD: glucose-6-phosphate dehydrogenase; CBC: complete blood count.

Graphic 101543 Version 5.0

Partial list of medicines and other substances thought to be unsafe or safe in individuals with G6PD deficiency

Medicines and other substances likely to be UNSAFE in moderate to severe G6PD deficiency*
Medications
Chlorpropamide
Dabrafenib
Dapsone (diaminodiphenyl sulfone)
Fluoroquinolones (ciprofloxacin, moxifloxacin, norfloxacin, ofloxacin)¶
Methylene blue (methylthioninium chloride)Δ
Nalidixic acid◇
Nitrofurantoin, nifuratel, and nitrofurazone (nitrofural)◇
Phenazopyridine (pyridium)
Primaquine and tafenoquine
Rasburicase and pegloticase
Sulfonylureas (eg, glipizide, glyburide [glibenclamide])
Chemical exposures and foods
Fava beans
Henna compounds (black and red Egyptian)
Naphthalene (mothballs, lavatory deodorant)
Phenylhydrazine
"RUSH" (isobutyl nitrite, amyl nitrite)
Medicines that are PROBABLY SAFE given in usual therapeutic doses in G6PD deficiency*; NOTE: some of these were previously considered unsafe; safety in Class I variants is generally not known
Acetaminophen (Tylenol, Paracetamol)
Aminophenazone, dipyrone, and metamizole (NSAIDs)◇
Antazoline (antihistamine)
Antipyrine (phenazone)
Ascorbic acid (vitamin C)
Aspirin (acetylsalicylic acid)
Benzhexol (Artane)
Chloramphenicol
Chloroquine and hydroxychloroquine

Colchicine
Clotrimazole
Diphenhydramine (Benadryl)
Isoniazid
Levodopa (L-Dopa) and levodopa-carbidopa
Para-aminosalicylic acid
Para-aminobenzoic acid (PABA)
Phenylbutazone
Phenytoin
Probenecid (Benemid)
Procainamide (Pronestyl)
Pyrimethamine (Daraprim)
Quinine
Streptomycin
Sulfa-containing drugs§ (sulfacetamide, sulfadiazine, sulfamethoxazole [Gantanol], trimethoprim-sulfamethoxazole, sulfamethoxypyridazine [Kynex], sulfanilamide, sulfisoxazole [Gantrisin])
Tiaprofenic acid
Trimethoprim
Tripelennamine (Pyribenzamine)
Vitamin K

This is a general list and may not apply to all G6PD-deficient individuals. Use clinical judgment, and refer to UpToDate discussions, patient history, and other resources for additional information.

G6PD: glucose-6-phosphate deficiency; NSAIDs: nonsteroidal antiinflammatory drugs.

* Applies to Class I, II, and III G6PD variants. However, note that there is marked variability in reports. This list is based on evidence supporting a clear association with drug-induced hemolysis. Individual characteristics (ie, degree of G6PD deficiency, dose, presence of infection) will determine actual safety or injury. Medicines known to be unsafe in G6PD deficiency that are no longer in clinical use are excluded from this list. In cases where the patient truly requires the medication and G6PD status is unknown, it may be appropriate to administer and monitor closely.

¶ Levofloxacin is not listed because some cases of hemolytic anemia with levofloxacin have been associated with a positive Coombs test.

Δ Methylene blue is a component of some combination urinary tract products.

◇ Not available in the United States.

§ Sulfamethoxazole is widely used. Some cases of hemolysis in individuals with G6PD deficiency have been reported. Use with caution.

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Graphic 74254 Version 25.0

Physical findings as clues to the etiology of anemia in children

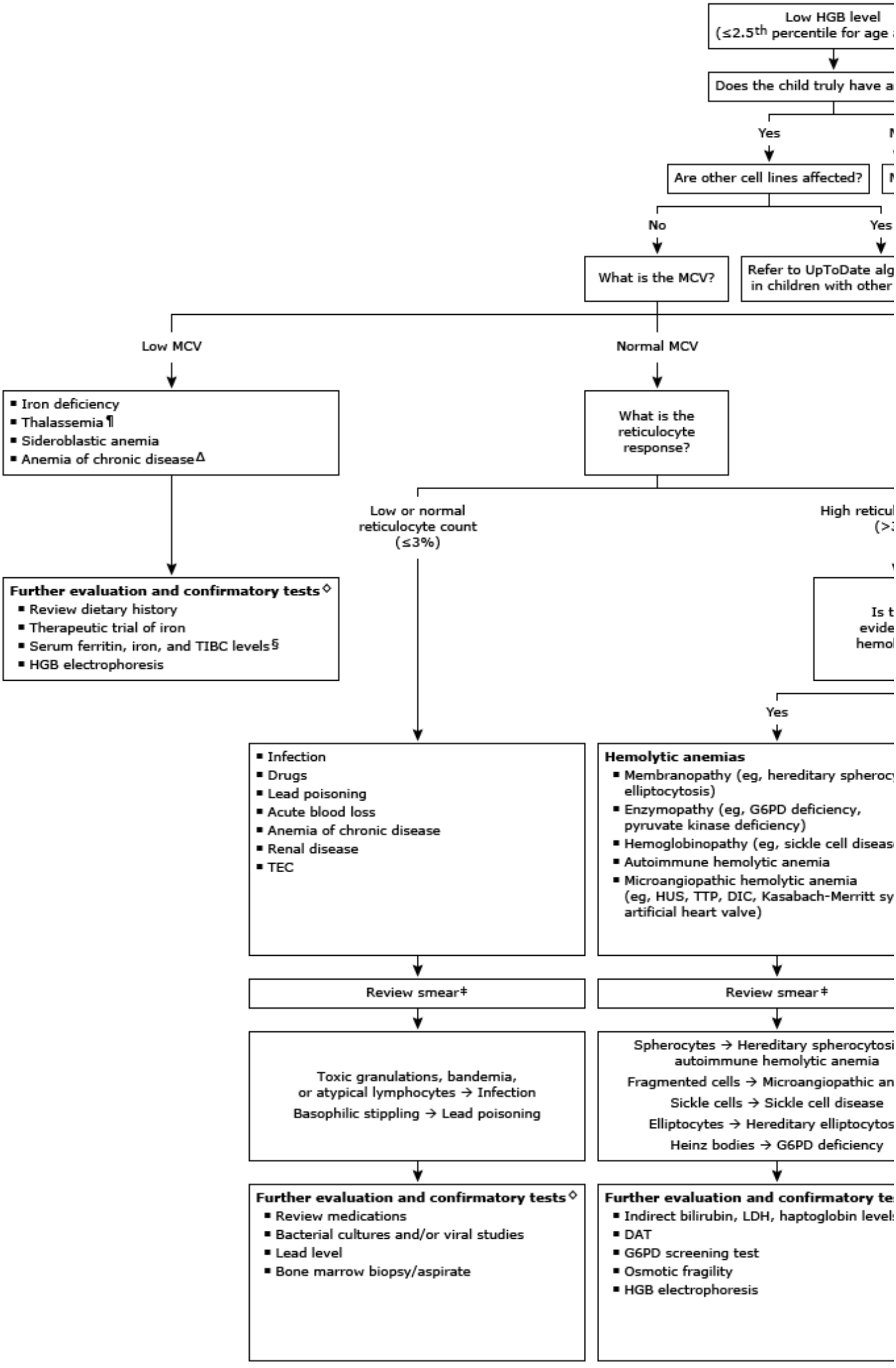
Finding	Possible etiology
Skin	
Hyperpigmentation	Fanconi anemia
Petechiae, purpura	Autoimmune hemolytic anemia with thrombocytopenia, hemolytic-uremic syndrome, bone marrow aplasia, bone marrow infiltration
Carotenemia	Suspect iron deficiency in infants
Jaundice	Hemolytic anemia, hepatitis, and aplastic anemia
Cavernous hemangioma	Microangiopathic hemolytic anemia
Ulcers on lower extremities	Sickle cell disease (S and C hemoglobinopathies), thalassemia
Facies	
Frontal bossing, prominence of the malar and maxillary bones	Congenital hemolytic anemias, thalassemia major, severe iron deficiency
Eyes	
Microcornea	Fanconi anemia
Tortuosity of the conjunctival and retinal vessels	Sickle cell disease (S and C hemoglobinopathies)
Microaneurysms of retinal vessels	Sickle cell disease (S and C hemoglobinopathies)
Cataracts	Glucose-6-phosphate dehydrogenase deficiency, galactosemia with hemolytic anemia in newborn period
Vitreous hemorrhages	S hemoglobinopathy
Retinal hemorrhages	Chronic, severe anemia
Edema of the eyelids	Infectious mononucleosis, exudative enteropathy with iron deficiency, renal failure
Blindness	Osteopetrosis
Mouth	
Glossitis	Vitamin B12 deficiency, iron deficiency
Angular stomatitis	
Chest	
Unilateral absence of the pectoral muscles	Poland syndrome (increased incidence of leukemia)
Shield chest	Diamond-Blackfan syndrome
Hands	

Triphalangeal thumbs	Red cell aplasia
Hypoplasia of the thenar eminence	Fanconi anemia
Spoon nails	Iron deficiency
Spleen	
Enlargement	Congenital hemolytic anemia, leukemia, lymphoma acute infection, portal hypertension

Reproduced with permission from: Oski FA, Brugnara G, Nathan DG. A diagnostic approach to the anemia patient. In: Nathan and Oski's Hematology of Infancy and Childhood. WB Sauders, Philadelphia. 1998. p.378.

Graphic 50361 Version 5.0

Diagnostic approach to isolated anemia in children: Morphologic classificatic


Low HGB level
(≤2.5th percentile for age
Does the child truly have a
Yes
Are other cell lines affected?
No
Yes
What is the MCV?
Refer to UpToDate alg
in children with other
Low MCV
Normal MCV
▪ Iron deficiency
▪ Thalassemia ¶
▪ Sideroblastic anemia
▪ Anemia of chronic disease Δ
What is the
reticulocyte
response?
Low or normal
reticulocyte count
(≤3%)
High reticul
(>
Is t
evide
hemol
Further evaluation and confirmatory tests ◇
▪ Review dietary history
▪ Therapeutic trial of iron
▪ Serum ferritin, iron, and TIBC levels §
▪ HGB electrophoresis
Yes
▪ Infection
▪ Drugs
▪ Lead poisoning
▪ Acute blood loss
▪ Anemia of chronic disease
▪ Renal disease
▪ TEC
Hemolytic anemias
▪ Membranopathy (eg, hereditary spheroc
elliptocytosis)
▪ Enzymopathy (eg, G6PD deficiency,
pyruvate kinase deficiency)
▪ Hemoglobinopathy (eg, sickle cell diseas
▪ Autoimmune hemolytic anemia
▪ Microangiopathic hemolytic anemia
(eg, HUS, TTP, DIC, Kasabach-Merritt sy
artificial heart valve)
Review smear ‡
Review smear ‡
Toxic granulations, bandemia,
or atypical lymphocytes → Infection
Basophilic stippling → Lead poisoning
Spherocytes → Hereditary spherocytosi
autoimmune hemolytic anemia
Fragmented cells → Microangiopathic an
Sickle cells → Sickle cell disease
Elliptocytes → Hereditary elliptocytos
Heinz bodies → G6PD deficiency
Further evaluation and confirmatory tests ◇
▪ Review medications
▪ Bacterial cultures and/or viral studies
▪ Lead level
▪ Bone marrow biopsy/aspirate
Further evaluation and confirmatory te
▪ Indirect bilirubin, LDH, haptoglobin level
▪ DAT
▪ G6PD screening test
▪ Osmotic fragility
▪ HGB electrophoresis

HGB: hemoglobin; MCV: mean corpuscular volume; TIBC: total iron-binding capacity; TEC: transient eryth
dehydrogenase; HUS: hemolytic uremic syndrome; TTP: thrombotic thrombocytopenic purpura; DIC: diss
polymorphonuclear cells; LDH: lactate dehydrogenase; DAT: direct antiglobulin test; RDW: red cell distribu

* HGB levels in children vary considerably by age. During adolescence, HGB values also differ according t
values should be compared with age- and sex-adjusted norms. Mild anemia occurring at 6 to 9 weeks of l
pathologic. Falsely elevated HGB values may occur when measured using capillary samples (eg, finger or
measurements. Spurious results may also occur with automated counters in the presence of lipemia, her

¶ The RDW can be helpful in differentiating thalassemia from iron deficiency. High RDW is typical of iron d
thalassemia (though elevated RDW can occur).

Δ Anemia of chronic disease typically presents as a normocytic anemia but can have low MCV.

◇ Selected testing is based upon review of the patient's history and examination of the peripheral blood s

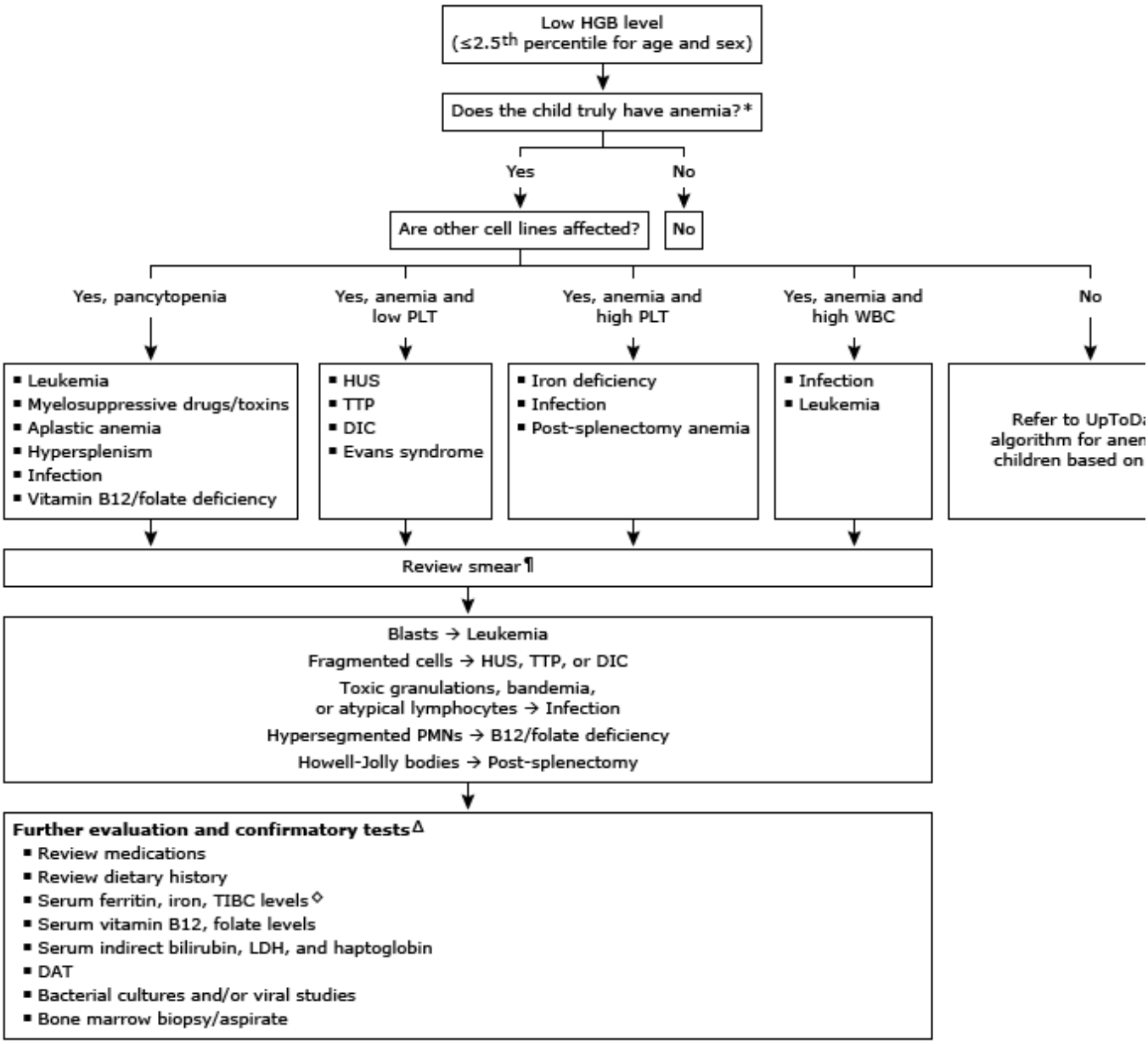
§ In children with mild microcytic anemia and dietary history that is suggestive of iron deficiency, serum i
necessary. In these children, a therapeutic trial of iron can be used to confirm the diagnosis.

¥ Evidence of hemolysis includes jaundice, indirect hyperbilirubinemia, elevated lactate dehydrogenase, a

‡ Findings on blood smear may suggest an underlying etiology of anemia, but they are generally not diag
confirm the diagnosis.

Graphic 101548 Version 7.0

Diagnostic approach to the child with anemia and abnormalities of other cell



HGB: hemoglobin; MCV: mean corpuscular volume; PLT: platelets; HUS: hemolytic uremic syndrome; TTP: thrombotic thrombocytopenic purpura; DIC: disseminated intravascular coagulation; WBC: white blood c PMNs: polymorphonuclear cells; TIBC: total iron-binding capacity; LDH: lactate dehydrogenase; DAT: direc antiglobulin test.

* HGB levels in children vary considerably by age. During adolescence, HGB values also differ according t When diagnosing anemia in pediatric patients, HGB values should be compared with age- and sex-adjust norms. Mild anemia occurring at 6 to 9 weeks of life is consistent with "physiologic anemia" and is not pathologic. Falsely elevated HGB values may occur when measured using capillary samples (eg, finger or sticks), particularly when using microhematocrit measurements. Spurious results may also occur with automated counters in the presence of lipemia, hemolysis, leukocytosis, or high immunoglobulin levels.

¶ Findings on blood smear may suggest an underlying etiology of anemia, but they are generally not diag Further confirmatory testing should be performed to confirm the diagnosis.

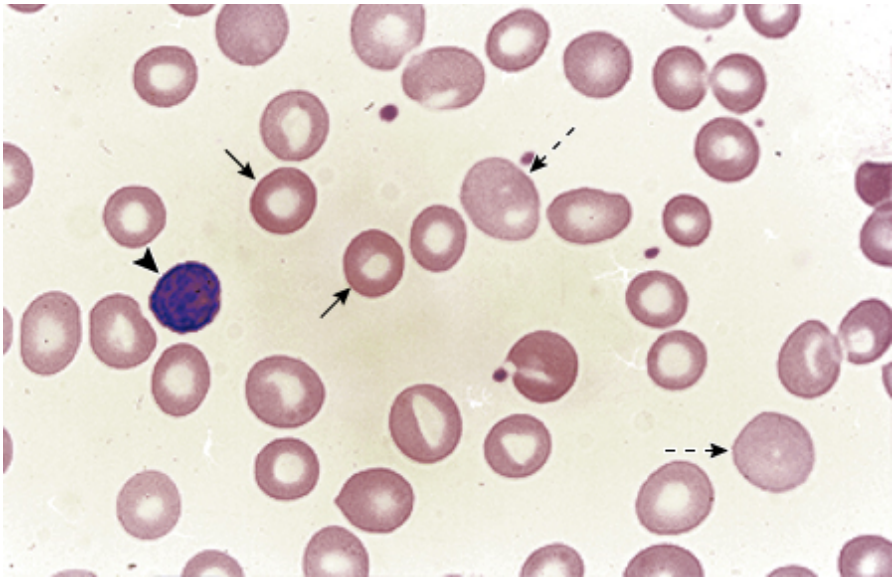
Δ Selected testing is based upon review of the patient's history and examination of the peripheral blood s

◇ In children with mild microcytic anemia with thrombocytosis and a dietary history that is suggestive of deficiency, serum iron studies (ie, ferritin, iron, and TIBC levels) are generally not necessary. In these child

therapeutic trial of iron can be used to confirm the diagnosis.

Graphic 101546 Version 6.0

Polychromatophilia due to increased reticulocytes

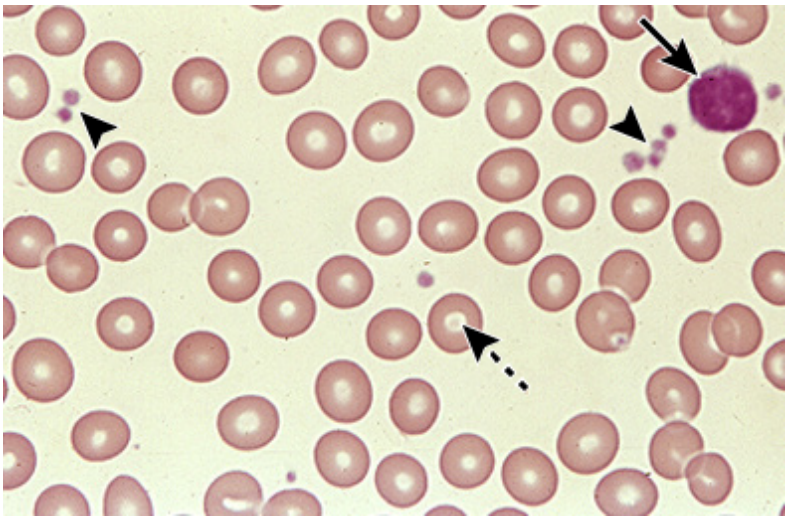


Peripheral blood smear taken from a patient with increased reticulocytes. Unlike mature red cells (arrows), which have central pallor and are the same size as the nucleus of a small lymphocyte (arrowhead), reticulocytes (dashed arrows) are larger, have a blue tint, and lack central pallor because they are not biconcave discs. (Wright-Giemsa stain.)

Courtesy of Stanley Schrier, MD.

Graphic 67042 Version 5.0

Normal peripheral blood smear



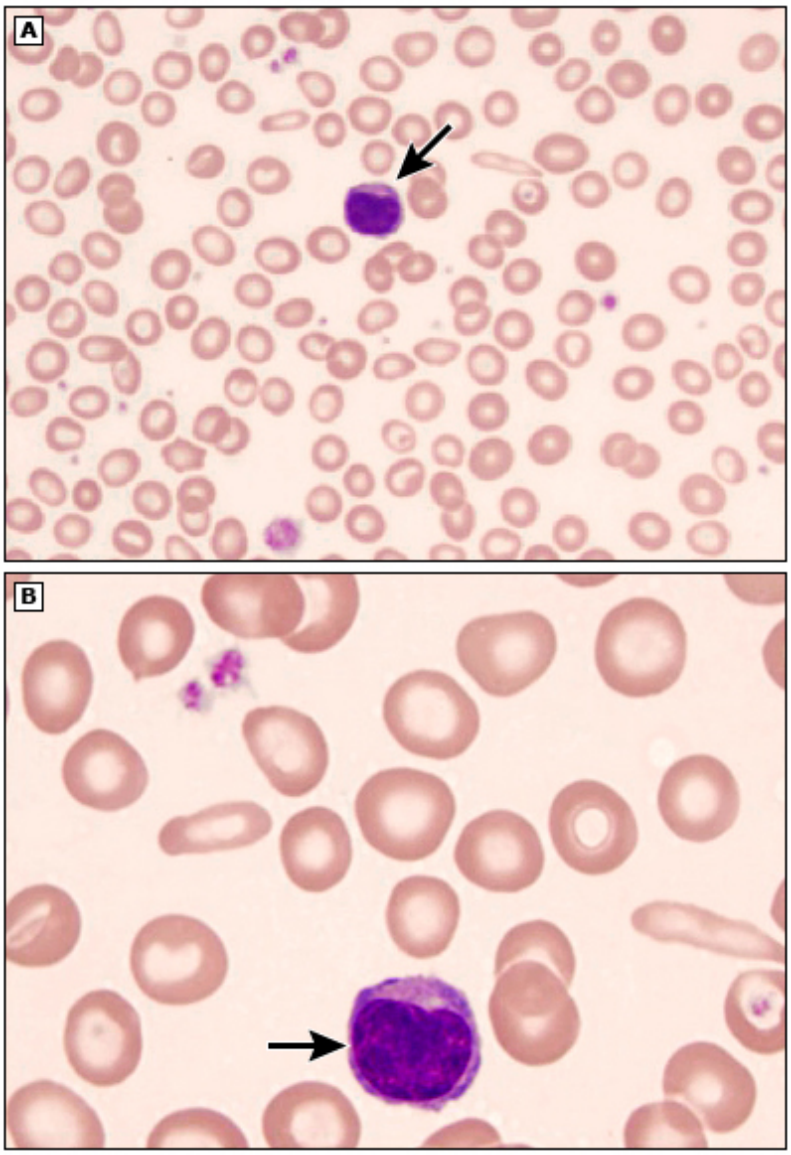
High-power view of a normal peripheral blood smear. Several platelets (arrowheads) and a normal lymphocyte (arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of

the nucleus of the small lymphocyte; central pallor (dashed arrow) should equal one-third of its diameter.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 5.0

Peripheral blood smear in iron deficiency anemia showing microcytic, hypochromic red blood cells

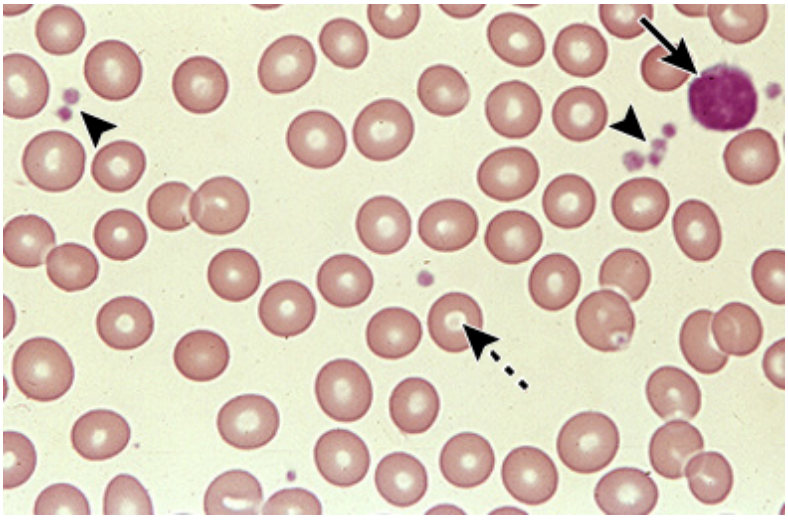


The same peripheral blood smear from a patient with iron deficiency is shown at two different magnifications. Small (microcytic) red blood cells are shown, many of which have a thin rim of pink hemoglobin (hypochromia). Occasional "pencil"-shaped cells are also present. A small lymphocyte is shown for size comparison (arrow). Normal red blood cells are similar in size to the nucleus of a small lymphocyte (arrow), and central pallor in normal red blood cells should equal approximately one-third of the cell diameter.

Kindly supplied by Dr. German Pihan, Department of Pathology, Beth Israel Deaconess Medical Center, Boston, MA.

Graphic 64267 Version 8.0

Normal peripheral blood smear

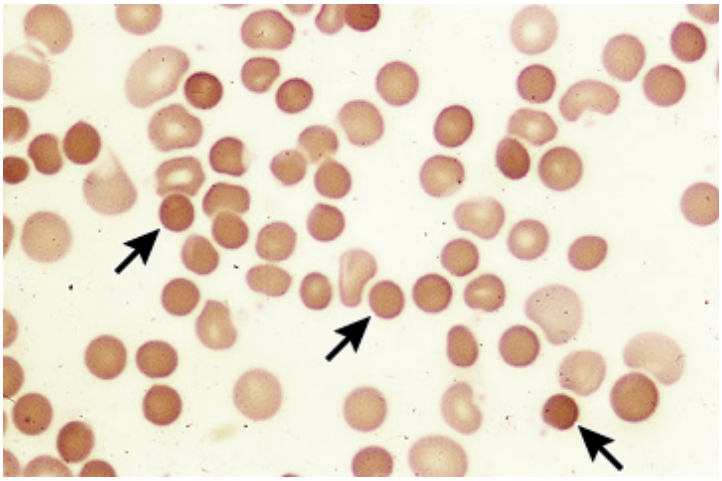


High-power view of a normal peripheral blood smear. Several platelets (arrowheads) and a normal lymphocyte (arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (dashed arrow) should equal one-third of its diameter.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 5.0

Spherocytes

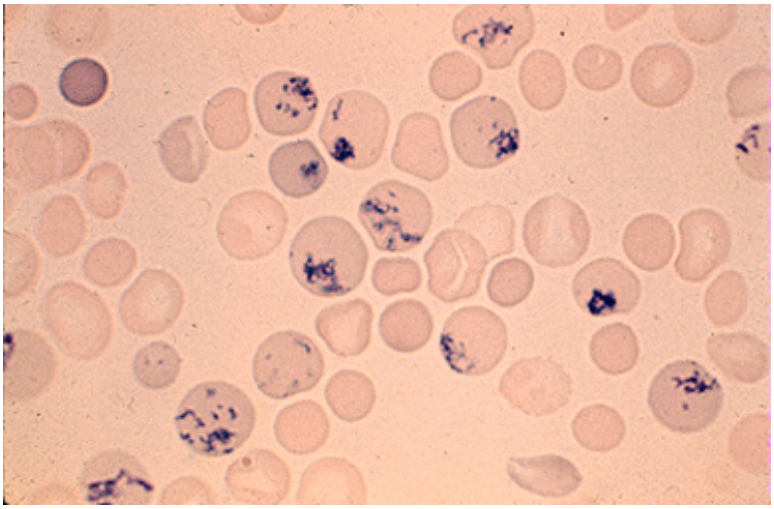


Peripheral blood smear shows multiple spherocytes, which are small, dark, dense hyperchromic red cells without central pallor (arrows). These findings are compatible with hereditary spherocytosis or autoimmune hemolytic anemia.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 70611 Version 5.0

Reticulocytes after supravital staining

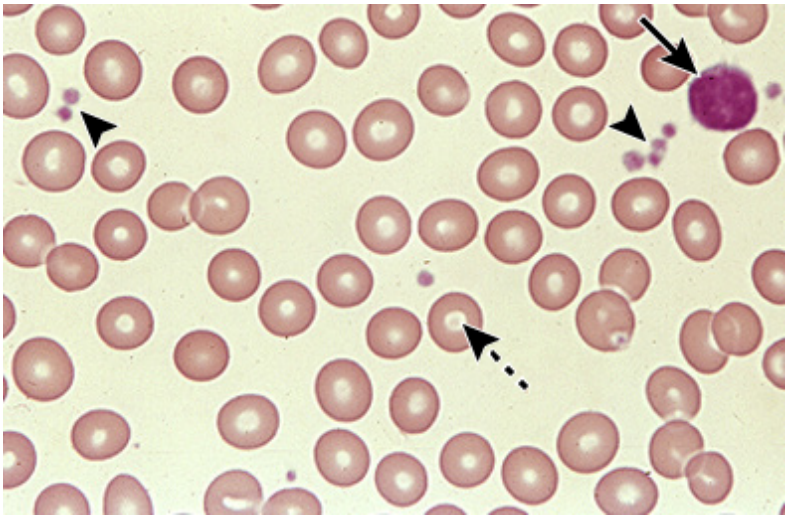


Supravital stain of a peripheral blood smear shows blue-stained residual reticulin (ribosomal RNA) in reticulocytes.

Courtesy of Stanley L Schrier, MD.

Graphic 74294 Version 3.0

Normal peripheral blood smear

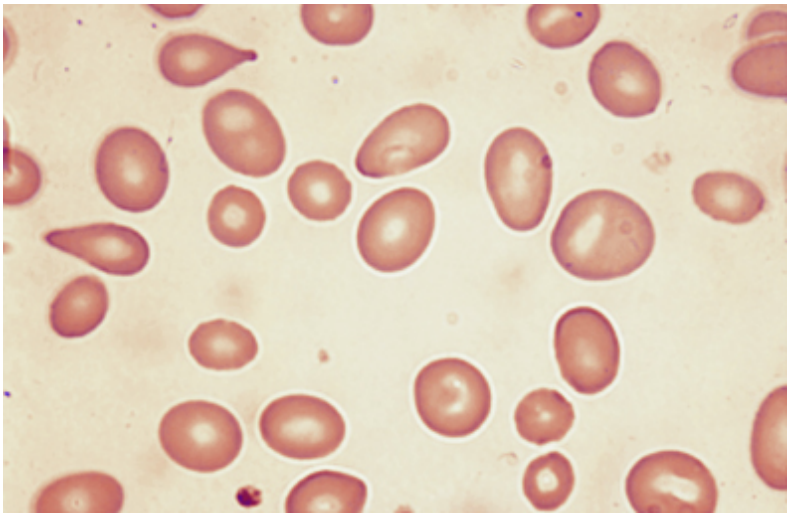


High-power view of a normal peripheral blood smear. Several platelets (arrowheads) and a normal lymphocyte (arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (dashed arrow) should equal one-third of its diameter.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 5.0

Macro-ovalocytes in vitamin B12 deficiency

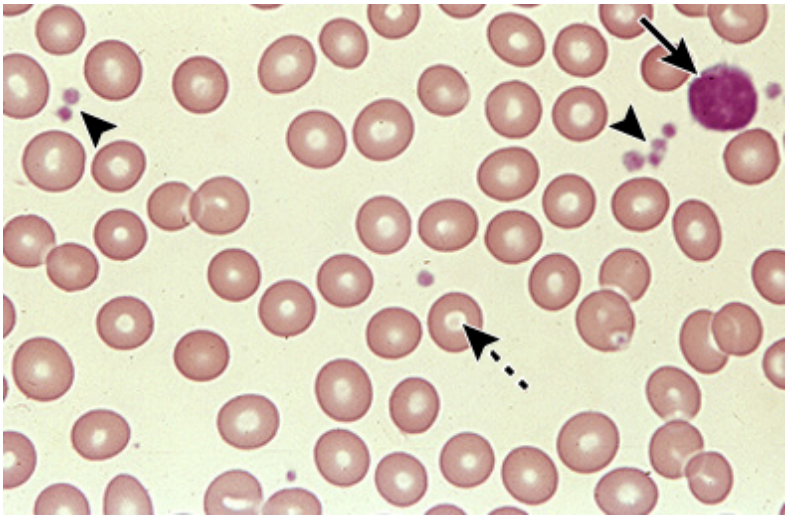


Peripheral smear shows marked macro-ovalocytosis in a patient with vitamin B12 deficiency. In this case, teardrop cells are an advanced form of macro-ovalocytes.

Courtesy of Stanley L Schrier, MD.

Graphic 74901 Version 6.0

Normal peripheral blood smear

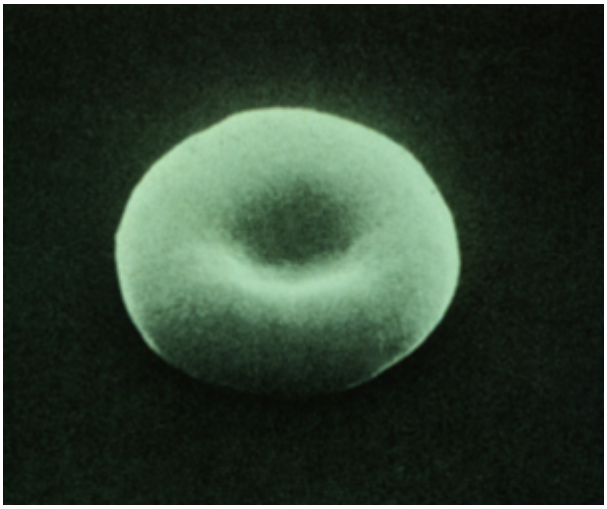


High-power view of a normal peripheral blood smear. Several platelets (arrowheads) and a normal lymphocyte (arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (dashed arrow) should equal one-third of its diameter.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 5.0

Normal red blood cell

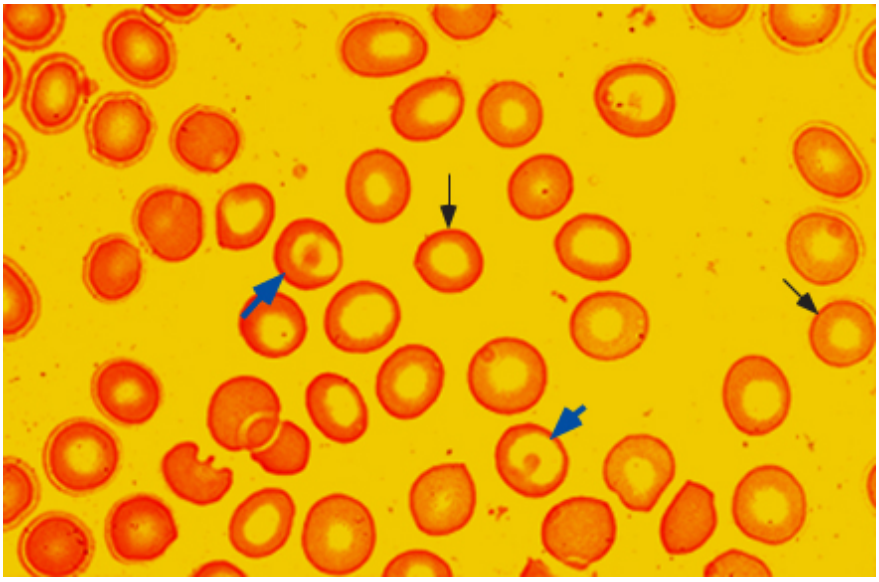


Scanning electron microphotograph of a normal adult human red blood cell. Note the biconcave disc shape, which gives the cell more surface area than a sphere of identical volume. The normal red cell is thinnest in the center, resulting in the central pallor seen on the peripheral smear.

Courtesy of Stanley L Schrier, MD.

Graphic 72999 Version 1.0

Beta thalassemia trait

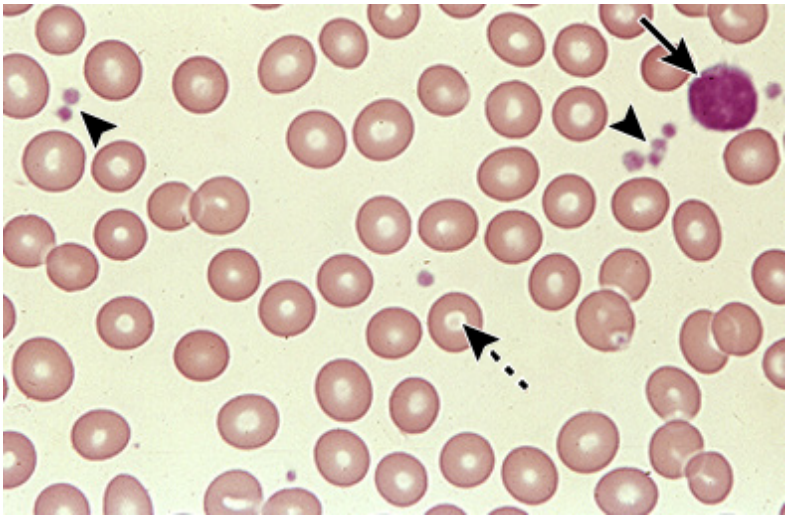


Peripheral smear from a patient with beta thalassemia trait. The field shows numerous hypochromic and microcytic red cells (thin arrows), some of which are also target cells (blue arrows).

Courtesy of Stanley Schrier, MD

Graphic 56728 Version 1.0

Normal peripheral blood smear

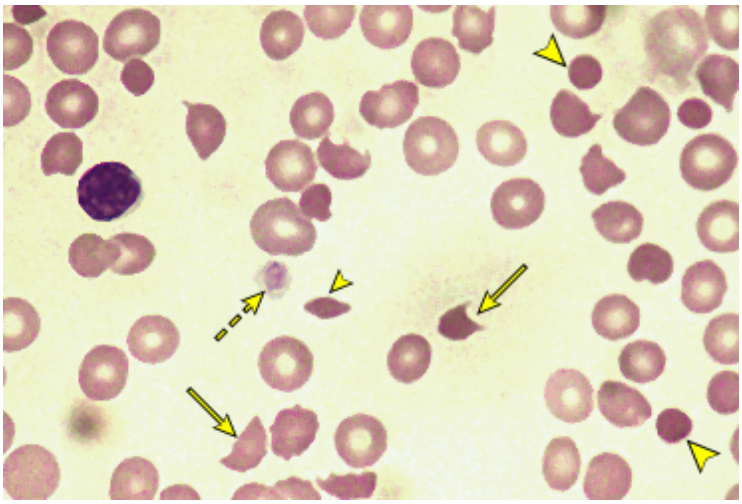


High-power view of a normal peripheral blood smear. Several platelets (arrowheads) and a normal lymphocyte (arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (dashed arrow) should equal one-third of its diameter.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 5.0

Peripheral smear in microangiopathic hemolytic anemia showing presence of schistocytes

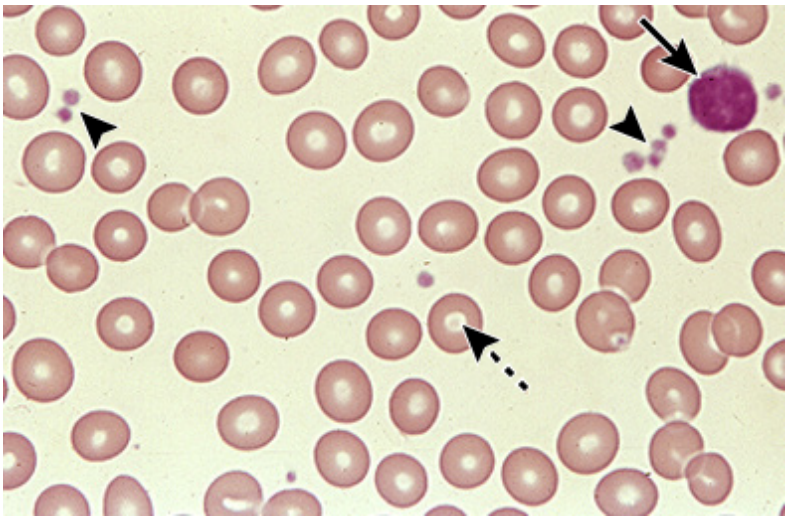


Peripheral blood smear from a patient with a microangiopathic hemolytic anemia with marked red cell fragmentation. The smear shows multiple helmet cells (arrows) and other fragmented red cells (small arrowhead); microspherocytes are also seen (large arrowheads). The platelet number is reduced; the large platelet in the center (dashed arrow) suggests that the thrombocytopenia is due to enhanced destruction.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 70851 Version 8.0

Normal peripheral blood smear



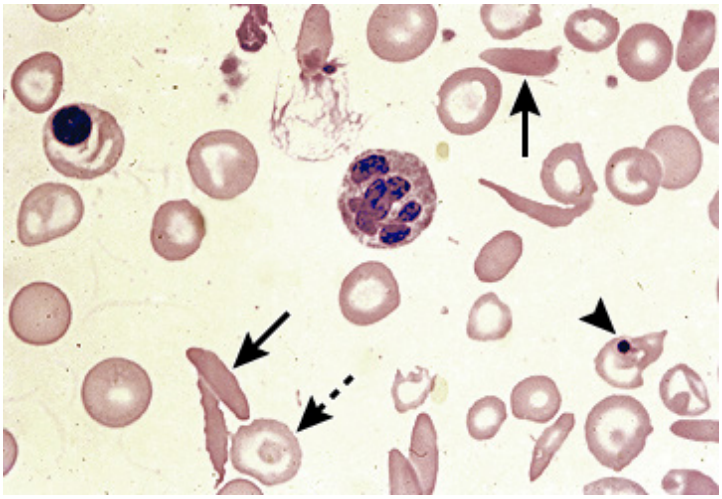
High-power view of a normal peripheral blood smear. Several platelets (arrowheads) and a normal lymphocyte (arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of

the nucleus of the small lymphocyte; central pallor (dashed arrow) should equal one-third of its diameter.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 5.0

Peripheral blood smear in sickle cell anemia

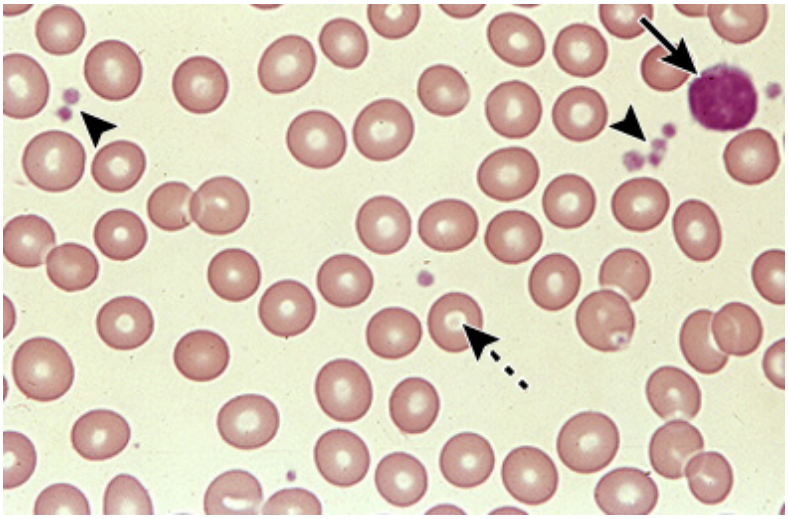


Peripheral blood smear from a patient with sickle cell anemia. This smear shows multiple sickle cells (arrows). There are also findings consistent with functional asplenia, including a nucleated red blood cell (upper left), a red blood cell containing a Howell-Jolly body (arrowhead), and target cells (dashed arrow).

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 64449 Version 10.0

Normal peripheral blood smear

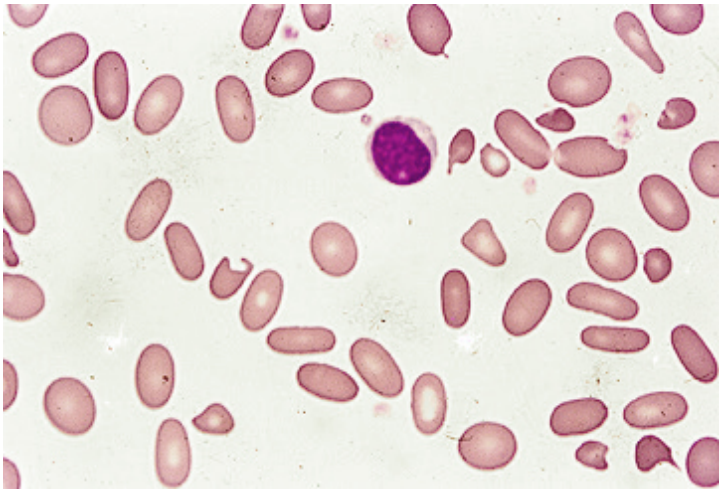


High-power view of a normal peripheral blood smear. Several platelets (arrowheads) and a normal lymphocyte (arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (dashed arrow) should equal one-third of its diameter.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 5.0

Elliptical red cells in hereditary elliptocytosis

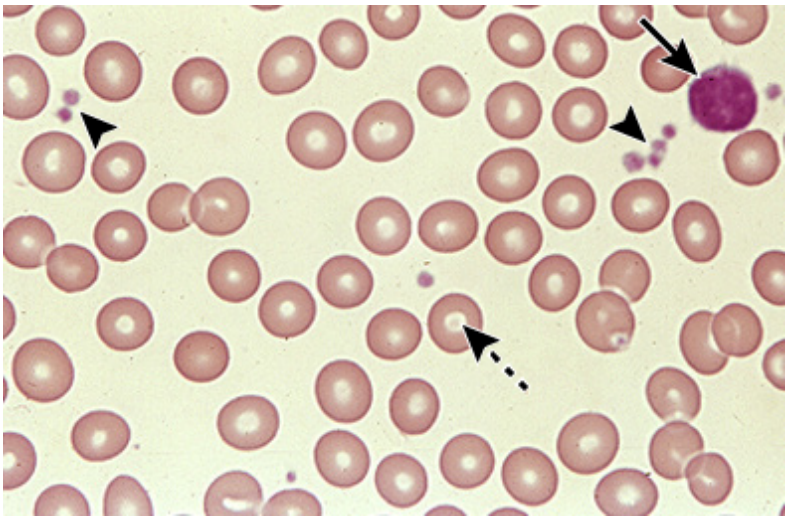


Peripheral blood smear from a patient with hereditary elliptocytosis shows multiple elliptocytes.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 63129 Version 4.0

Normal peripheral blood smear

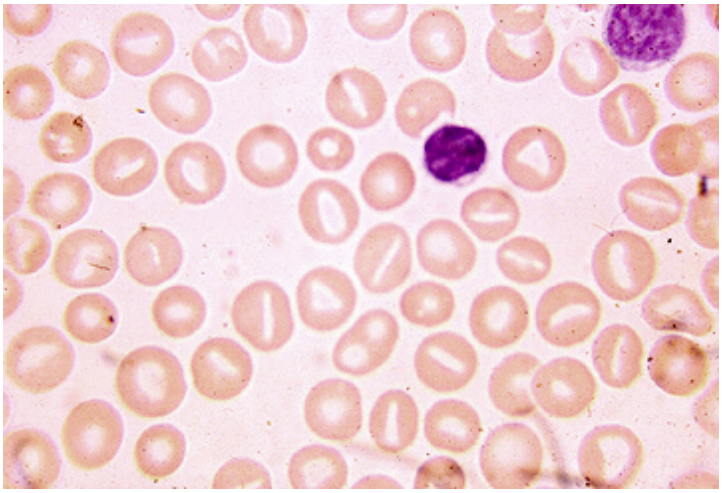


High-power view of a normal peripheral blood smear. Several platelets (arrowheads) and a normal lymphocyte (arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (dashed arrow) should equal one-third of its diameter.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 5.0

Stomatocytosis

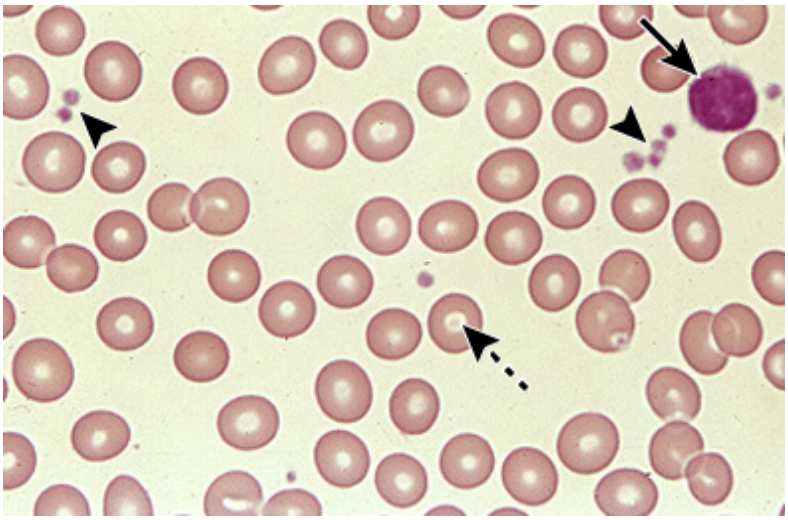


Peripheral blood smear showing multiple stomatocytes characterized by a mouth-shaped area of central pallor.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 75535 Version 2.0

Normal peripheral blood smear

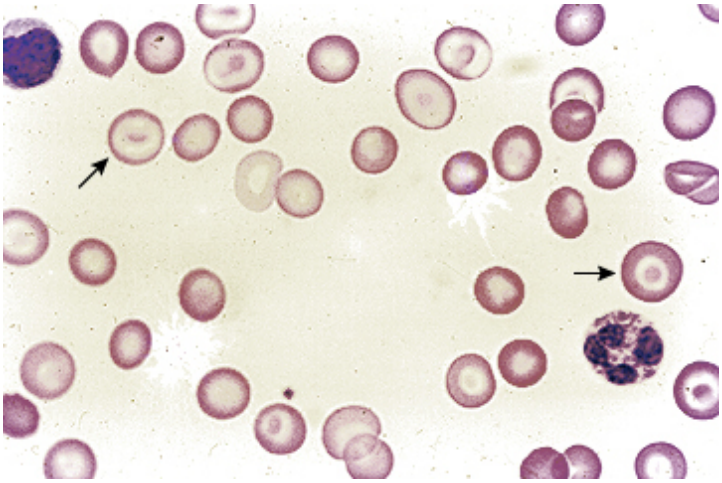


High-power view of a normal peripheral blood smear. Several platelets (arrowheads) and a normal lymphocyte (arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (dashed arrow) should equal one-third of its diameter.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 5.0

Target cells

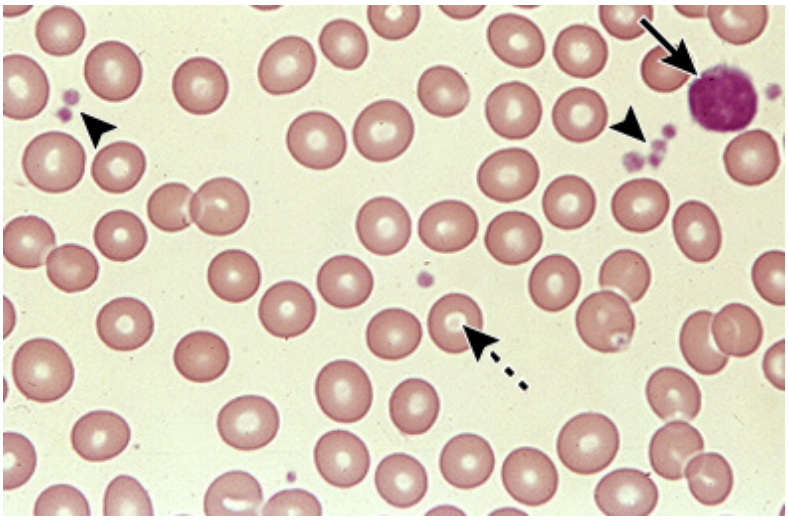


Peripheral smear shows multiple target cells that have an area of central density surrounded by a halo of pallor (arrows). These cells are characteristic of liver disease and certain hemoglobinopathies (most notably hemoglobin C disease).

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 80318 Version 3.0

Normal peripheral blood smear

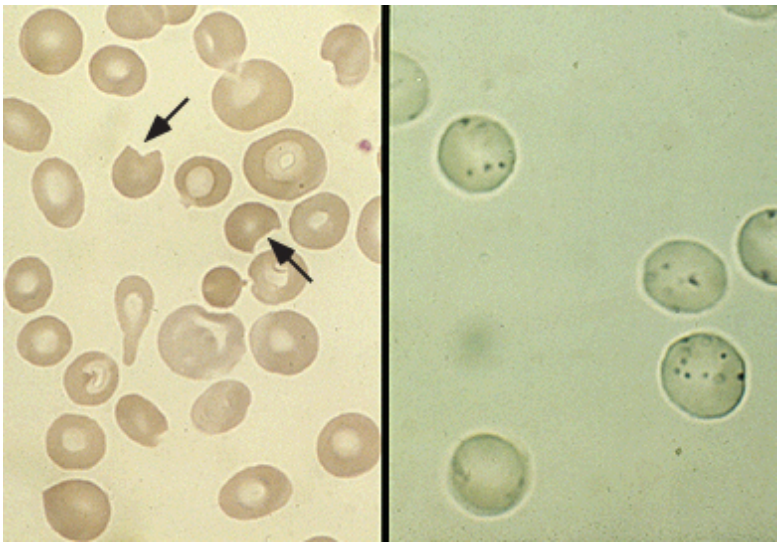


High-power view of a normal peripheral blood smear. Several platelets (arrowheads) and a normal lymphocyte (arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (dashed arrow) should equal one-third of its diameter.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 5.0

Peripheral smear in Heinz body hemolytic anemia showing Heinz bodies and bite cells



Images of a peripheral blood smear from a patient with Heinz body hemolytic anemia.

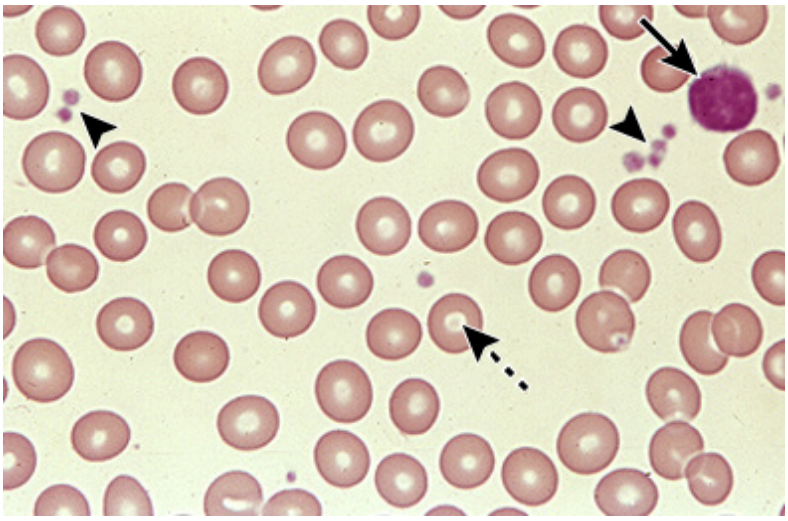
(Left panel) Red blood cells with characteristic bite-like deformity (left arrow) and a blister cell with hemoglobin puddled to one side (right arrow).

(Right panel) Heinz body preparation that reveals the denatured hemoglobin precipitates.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 73790 Version 9.0

Normal peripheral blood smear



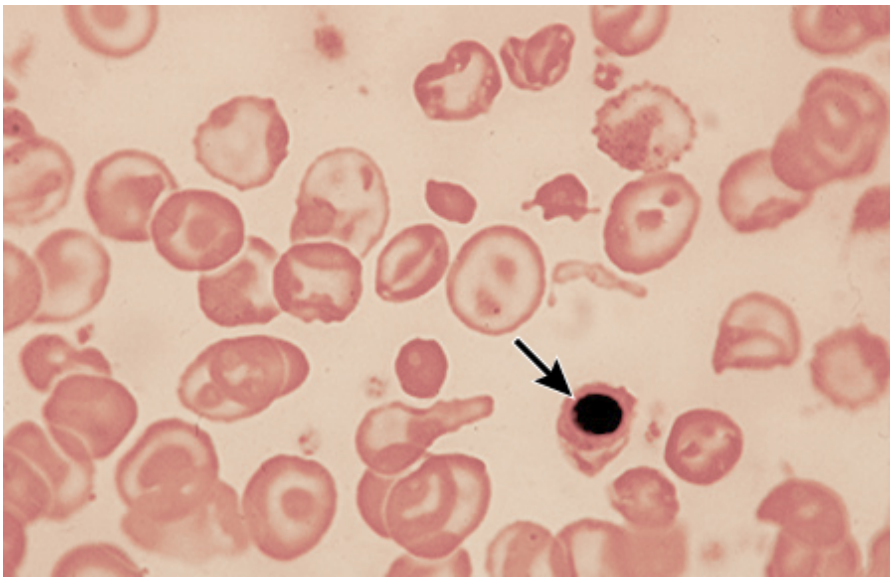
High-power view of a normal peripheral blood smear. Several platelets (arrowheads) and a normal lymphocyte (arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of

the nucleus of the small lymphocyte; central pallor (dashed arrow) should equal one-third of its diameter.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 5.0

Peripheral blood smear in beta thalassemia intermedia

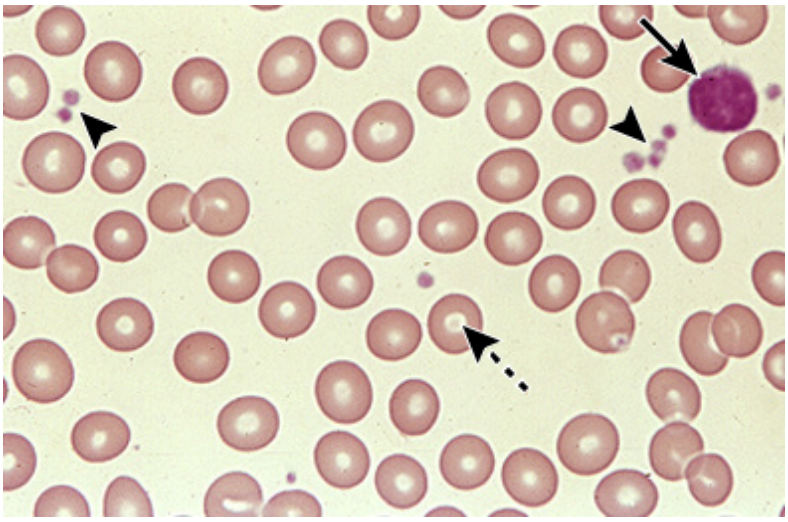


Peripheral smear from a patient with beta thalassemia intermedia postsplenectomy. This field shows target cells, hypochromic cells, microcytic cells, red cell fragments, red cells with bizarre shapes, and a single nucleated red cell (arrow).

Courtesy of Stanley Schrier, MD.

Graphic 76666 Version 4.0

Normal peripheral blood smear

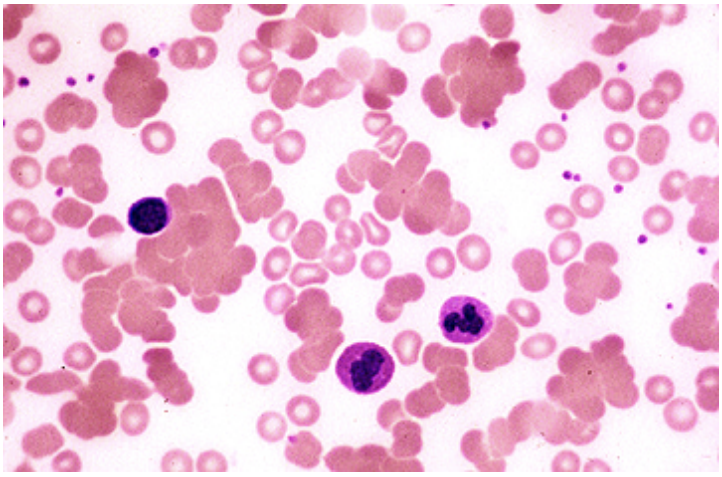


High-power view of a normal peripheral blood smear. Several platelets (arrowheads) and a normal lymphocyte (arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (dashed arrow) should equal one-third of its diameter.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 5.0

Peripheral blood smear showing red blood cell agglutination in a patient with cold agglutinin disease

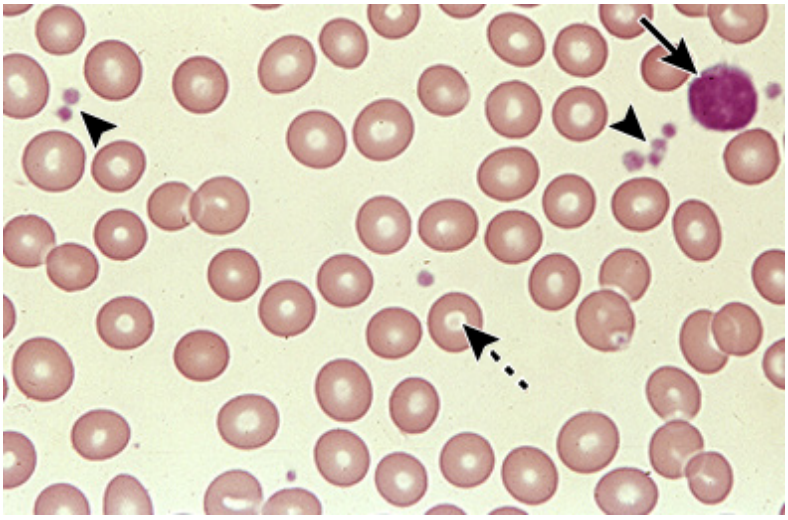


The blood smear shows marked red blood cell agglutination into irregular clumps.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 50522 Version 8.0

Normal peripheral blood smear

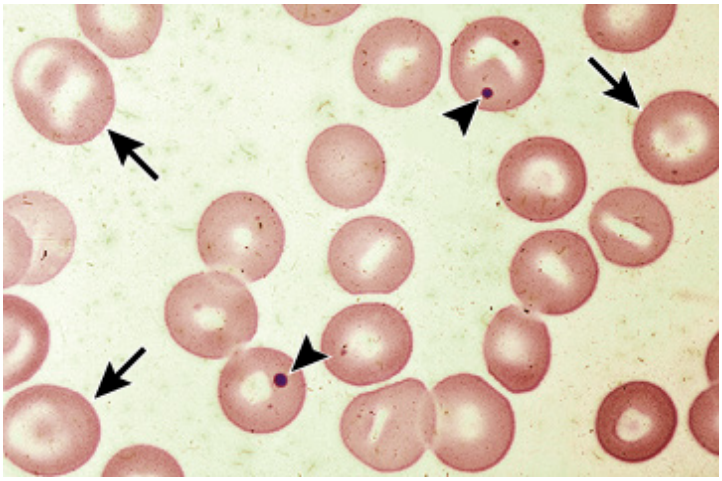


High-power view of a normal peripheral blood smear. Several platelets (arrowheads) and a normal lymphocyte (arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (dashed arrow) should equal one-third of its diameter.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 5.0

Howell-Jolly bodies



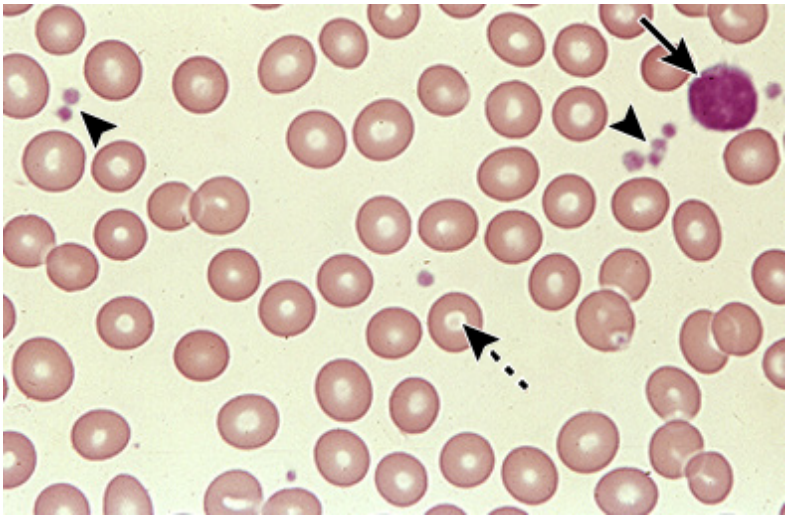
This peripheral blood smear shows 2 RBCs that contain Howell-Jolly bodies (arrowheads). Howell-Jolly bodies are remnants of RBC nuclei that are normally removed by the spleen. Thus, they are seen in patients who have undergone splenectomy (as in this case) or who have functional asplenia (eg, from sickle cell disease). Target cells (arrows) are another consequence of splenectomy.

RBC: red blood cell.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 60588 Version 10.0

Normal peripheral blood smear



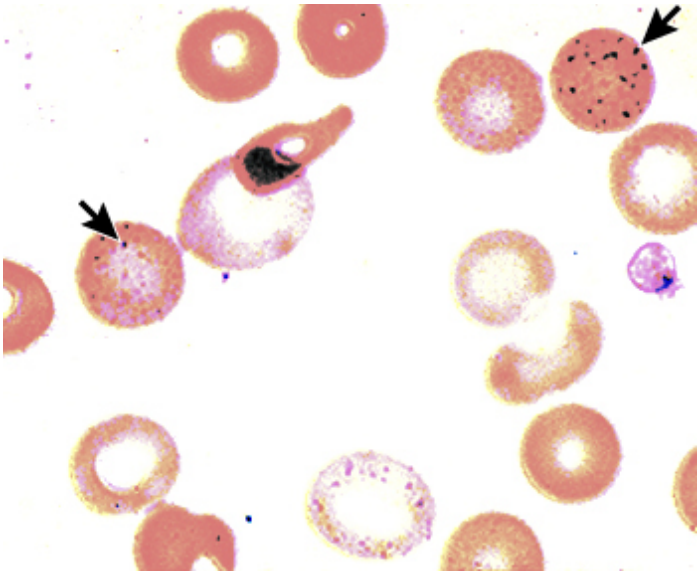
High-power view of a normal peripheral blood smear. Several platelets (arrowheads) and a normal lymphocyte (arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of

the nucleus of the small lymphocyte; central pallor (dashed arrow) should equal one-third of its diameter.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 5.0

Basophilic stippling of red cells in lead poisoning



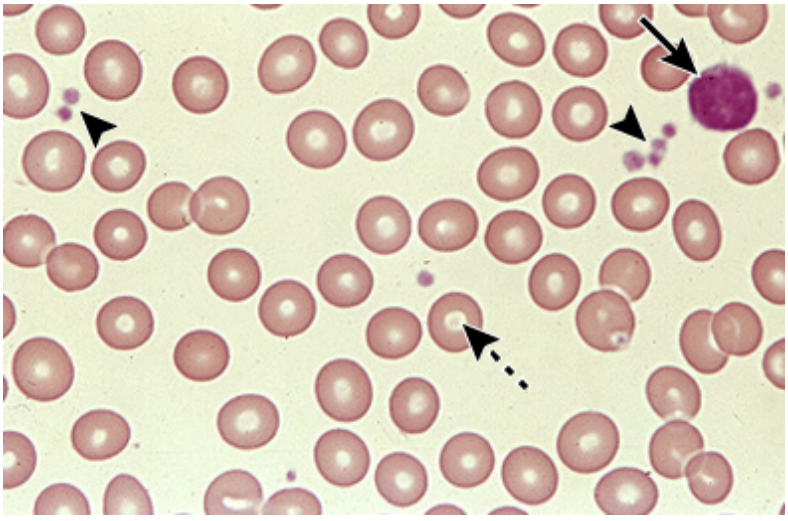
Peripheral blood smear shows basophilic stippling in several red cells from a patient with lead poisoning. The granules represent ribosomal precipitates. Other causes of basophilic stippling include:

- Thalassemia
- Megaloblastic anemia
- Sickle cell disease
- Sideroblastic anemia
- Heavy alcohol use
- Lead and other heavy metal poisoning
- Pyrimidine 5'-nucleotidase (P5N) deficiency

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 71989 Version 5.0

Normal peripheral blood smear



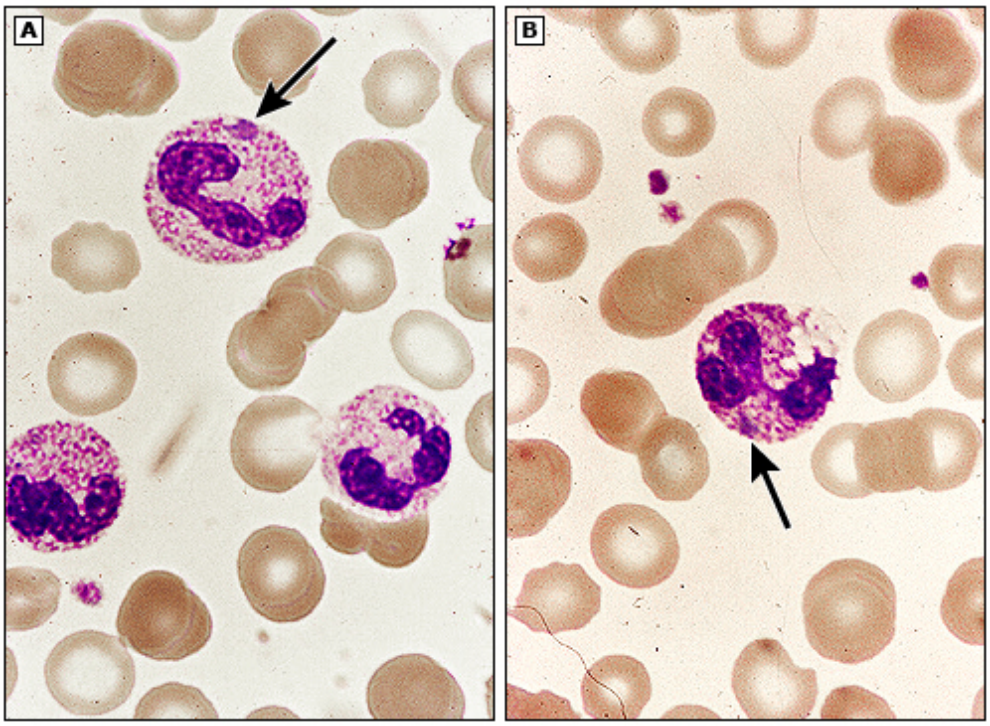
High-power view of a normal peripheral blood smear. Several platelets (arrowheads) and a normal lymphocyte (arrow) can also

be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (dashed arrow) should equal one-third of its diameter.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 59683 Version 5.0

Toxic granulations and Döhle bodies in infection/inflammation



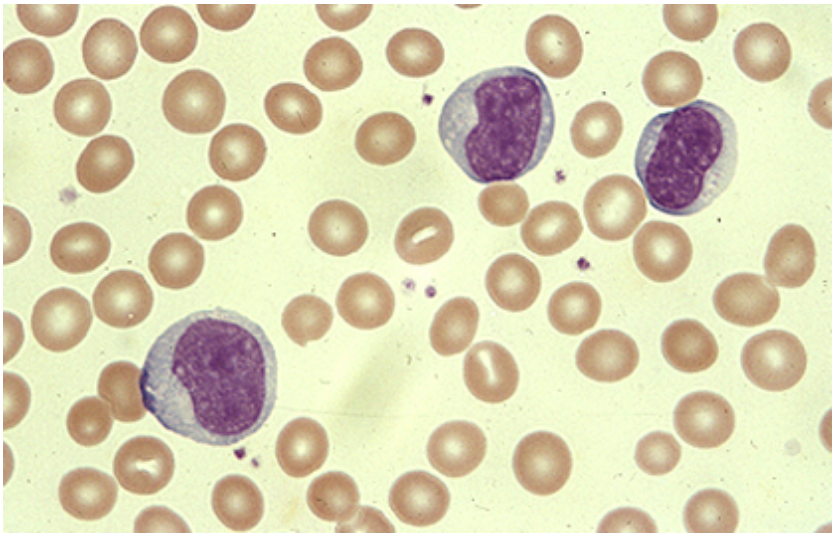
(A) Peripheral blood smear shows neutrophils with toxic granulations, which are dark coarse granules. A Döhle body is also seen (arrow).

(B) A neutrophil with toxic granulations, vacuoles (another toxic change), and a Döhle body (arrow). These abnormalities are characteristic of toxic systemic illnesses.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 70248 Version 4.0

Atypical lymphocytes in infectious mononucleosis

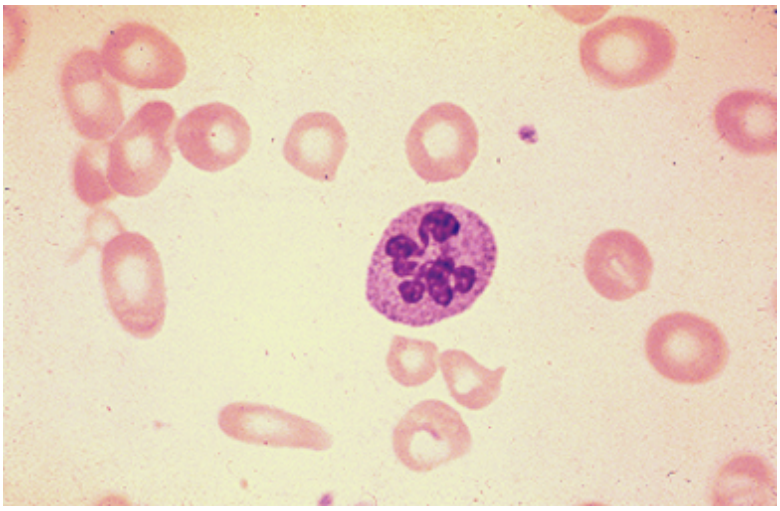


Peripheral smear from a patient with infectious mononucleosis shows three atypical lymphocytes with generous cytoplasm.

Courtesy of Carola von Kapff, SH (ASCP).

Graphic 55986 Version 2.0

Peripheral blood smear showing megaloblastic changes

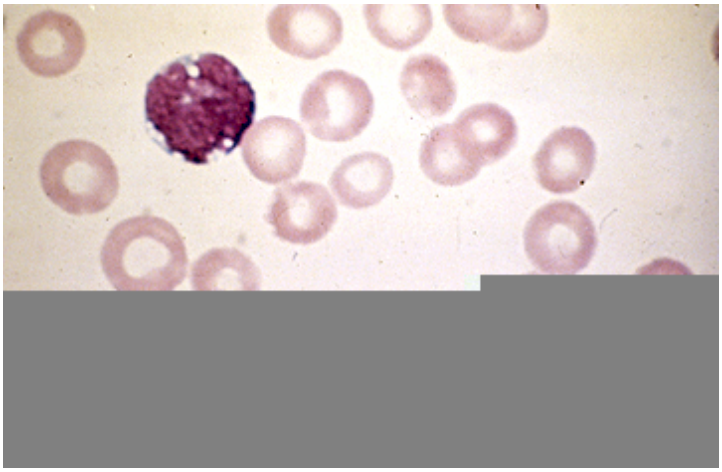


Peripheral blood smear showing a hypersegmented neutrophil (seven lobes) and macroovalocytes, a pattern that can be seen with vitamin B12 (cobalamin) or folate deficiency.

Courtesy of Stanley L Schrier, MD.

Graphic 58820 Version 5.0

Lymphoblasts in acute lymphoblastic leukemia



Blood smear showing small lymphoblasts with rare nucleoli and vacuoles, as seen in acute lymphocytic leukemia.

Courtesy of Robert Baehner, MD.

Graphic 57831 Version 5.0

Causes of hemolytic anemia in children

Intrinsic red blood cell defects
Hemoglobinopathies (eg, sickle cell disease, thalassemias)
Membrane defects (eg, hereditary spherocytosis, elliptocytosis)
Enzyme deficiencies (eg, G6PD, pyruvate kinase deficiencies)
Extrinsic hemolytic processes
Autoimmune hemolytic anemia (AIHA) ▪ Warm-reactive ▪ Cold agglutinin disease ▪ Paroxysmal cold hemoglobinuria
Hypersplenism
Systemic disease ▪ Infection (eg, malaria, *Clostridium perfringens)* ▪ Liver disease ▪ Renal disease
Drugs and toxins*
Microangiopathies ▪ Hemolytic uremic syndrome (HUS) ▪ Thrombotic thrombocytopenic purpura (congenital or acquired) ▪ Disseminated intravascular coagulation (DIC)
Mechanical damage (eg, artificial heart valves, Kasabach-Merritt phenomena)
Wilson disease
Combined mechanism (intrinsic and extrinsic)
Paroxysmal nocturnal hemoglobinuria (PNH)

G6PD: glucose-6-phosphate dehydrogenase.

* For details of specific agents, refer to separate UpToDate content on hemolytic anemia due to drugs and toxins.

Courtesy of Michael Recht, MD, PhD.

Graphic 64454 Version 11.0

Contributor Disclosures

Jacquelyn M Powers, MD, MS Consultant/Advisory Boards: Pharmacosmos LLC [Iron deficiency anemia]. All of the relevant financial relationships listed have been mitigated. **Claudio Sandoval, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Sarah O'Brien, MD, MSc** Grant/Research/Clinical Trial Support: Bristol Myers Squibb [Anticoagulation]. Consultant/Advisory Boards: AstraZeneca [Reversal agent for anticoagulation]; Bristol Myers Squibb [Anticoagulation]; Pharmacosmos [Intravenous iron]. All of the relevant financial relationships listed have been mitigated. **Martin I Lorin, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Carrie Armsby, MD, MPH** No relevant financial relationship(s) with ineligible companies to disclose.

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