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Guest Editor

PREFACE

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INTERPRETATION OF THE COMPLETE BLOOD COUNT

Mark C. Walters, MD, and Herbert T. Abelson, MD

BACKGROUND

The complete blood count (CBC) is a deceptively simple test to order and interpret. Because the test is relatively inexpensive and, in the past, part of "routine" admission or evaluation labwork, the results often are given only cursory appraisal. In most cases, the primary assessments of interest are whether the patient is anemic, whether the total and differential white blood cell counts support the diagnosis of infection, and whether the platelet count is in a range that has an impact on hemostasis; however, astute practitioners may use nuances and clues from the CBC in many clinical situations to guide additional diagnostic evaluation.

The CBC is a bargain; its cost can be much less than modern imaging studies, but like the modern imaging studies, its value is lost without appropriate analysis. Hematology is undergoing a transformation and is literally being reborn with, for example, the discovery and application of new glycoprotein hormones or blood growth factors that regulate proliferation, differentiation, and function of blood cells. Because of this explosion of new technology and information, understanding of and sophisticated use of the CBC will take on added importance.

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Measurement

The CBC consists of hemoglobin concentration, hematocrit (packed cell volume), mean corpuscular hemoglobin (MCH), MCH concentration (MCHC), mean corpuscular volume (MCV), erythrocyte count, leukocyte count, and platelet count. Depending on the method of measurement, these may be measured directly or derived from calculations of other measured values. Two basic technologies are used for routine CBC measurement: (1) electric impedance and (2) light scatter.[20] Electric impedance directly measures hemoglobin, MCV, and erythrocyte count, whereas MCH, MCHC, and hematocrit are derived from the following formulas:

$$\text{MCH} = \text{Hb (g/L)}/\text{RBC } (10^6/\mu\text{L})$$

$$\text{MCHC} = \text{Hb (g/dL)}/\text{HCT (\%)}$$

$$\text{HCT} = \text{MCV (fL)} \times \text{RBC } (10^6/\mu\text{L})$$

Hemoglobin concentration is measured by absorbance spectrophotometry and relies on complete lysis of erythrocytes. Erythrocyte counting and size determination are accomplished by passage of cells through an electric field created by direct current (Fig. 1). As the cells pass singly through the field, a small resistance is generated that is measured as a pulse height. From the pulse height, the size and number of erythrocytes are determined. These data are frequently plotted as a histogram in the typical modern Coulter-type electric impedance instrument (Fig. 2). In the histogram, the MCV is illustrated as well as the distribution of cells that give rise to the MCV. This measure of dispersion of the erythrocyte size distribution is called the RBC distribution width (RDW), which is the coefficient of variation of the erythrocyte volume distribution expressed as a percentage. The RDW provides information about cell size variability and is a sensitive means of detecting abnormal populations of erythrocytes that otherwise may go undetected, even with careful visual examination of the blood smear.

The fact that the hematocrit is calculated rather than measured directly accounts for differences that occur when "spun" and automated hematocrits are compared. The manual hematocrit is performed with a timed application of centrifugal force on a column of blood. The degree of erythrocyte packing that occurs with the application of this force is termed *optimal* rather than *complete,* because small pockets of plasma are trapped in the spaces between the incompletely packed erythrocytes. The amount of plasma that is trapped is estimated to be 3% under most conditions[16]; however, this fraction is not constant over the spectrum of hematocrit values and becomes larger as the hematocrit increases. In addition, alteration in erythrocyte shape, density, and stiffness affects the fraction of trapped plasma; for example, certain erythrocyte shapes, such as spherocytes, sickle erythrocytes, hypochromic cells, and reticulocytes, trap more plasma.[25] Therefore, the calculated automated hematocrit tends to be less than the spun hematocrit. To permit close correlation between the manual and automated hematocrits, a correction factor of approximately 3% is applied to the calculation of the hematocrit, providing close correlation unless deviation from normal values and erythrocyte shapes occurs as with polycythemia or spherocytosis. In these settings, the directly measured hemoglobin becomes a more reliable measurement for erythrocyte mass. A case can be made to dispense with reporting a calculated hematocrit with the CBC because the hemoglobin value that is measured directly is more reliable and is more closely related to oxygen-carrying capacity.

A simple "rule of 3s" for screening artifactual changes in erythrocyte measurements is the following: the measured hemoglobin concentration is approximately three times the RBC count, and the calculated hematocrit is three times the hemogobin value. When significant deviation occurs from these approximate calculations, artifacts in the CBC should be suspected.[21] Some of the more common artifacts are shown in

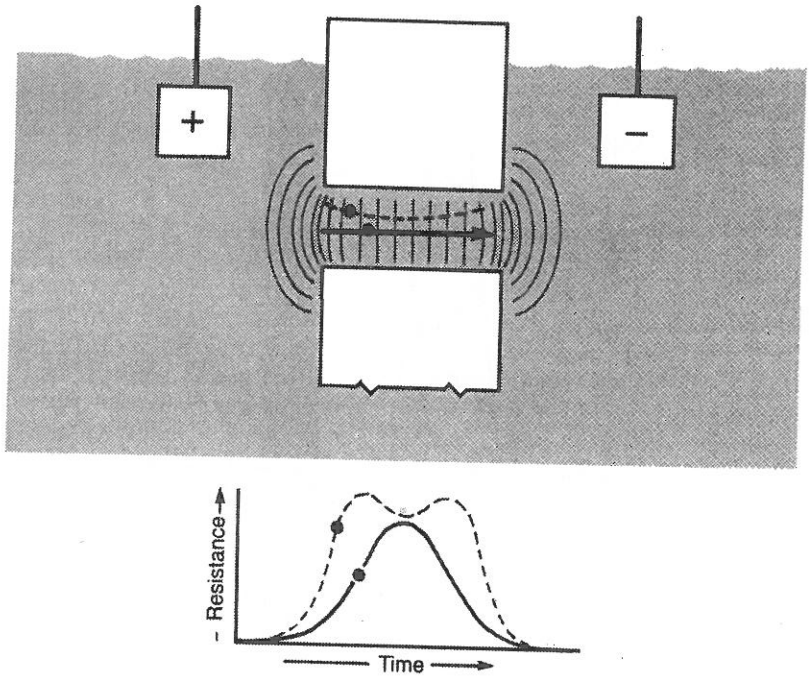

Figure 1. Electric impedance cell counting. Cells are passed through a small aperture to which an electric field has been applied. The cell generates a resistance that is measured as a pulse height as it passes through the field. Cells that do not follow a straight line through the field *(dotted line)* generate a bimodal pulse height. The cellular size is proportional to the pulse height, and both the size and number of cells are measured from the resistance that is generated. (*From* Haynes JL: Principles of flow cytometry. Cytometry 9(Suppl):7–17, © 1988; reprinted by permission of John Wiley & Sons, Inc.)

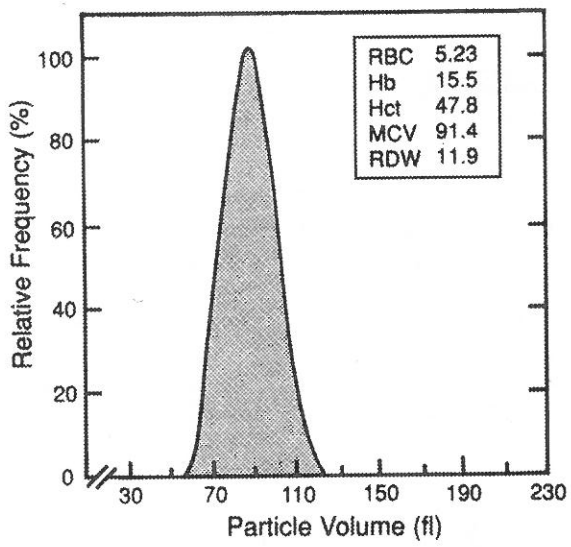

Figure 2. Erythrocyte volume distribution. Cell numbers, expressed as a relative frequency *(Y axis)* and cell volume *(X axis)*, are plotted in this idealized histogram from a Coulter-type electric impedance instrument. Mean corpuscular volume (MCV) and RBC distribution width (RDW), a measure of the dispersion of the volume distribution curve, are reported from these measurements. (*From* Bessman JD: Automated blood counts and differentials: A practical guide. Baltimore, Johns Hopkins University Press, 1986; reprinted by permission of the Johns Hopkins University Press.)

Table 1. For example, failure of complete cell lysis causes interference with hemoglobin measurement. This occurs in conditions that create hyperosmolar plasma (e.g., uremia). In this situation, the hematocrit and MCV are artificially elevated.

Agglutination of erythrocytes, which may occur in autoimmune hemolytic anemia because of cold-reacting IgM antibodies, also results in a markedly increased MCV unless precautions are taken to warm the blood thoroughly before analysis.[6] Elevated MCH and inaccurate hematocrit determination also may result. Another example is hyperleukocytosis (white blood cell count, $> 50{,}000/mm^3$), which can cause elevation of the hemoglobin, hematocrit, red blood cell count, and MCV.

Table 1. ARTIFACTS IN ELECTRONIC CELL COUNTING

Cause	Hb	Hct	RBC	MCV	MCH	MCHC
Cold agglutinins	—	—	↓	↑	↑	—
Hyperleukocytosis	↑	↑	↑	↑	—	—
Hyperosmolar plasma	—	↑	—	↑	—	↓

Blood Smear

The examination of the blood smear can be useful particularly in evaluating a patient with anemia. Unfortunately, to become facile in recognizing alterations in blood cell morphology, blood smears must be examined with regularity, a practice that is becoming rare in modern medicine. Nonetheless, several rules when examining the blood smear will assist in the evaluation of anemia. First, the smear must be adequate for examination. Inadequate smears can be especially problematic in very anemic or polycythemic patients. In these cases, concentration or dilution of the blood sample can improve the quality of the smear. The erythrocytes should exhibit central pallor rather than deform each other, as occurs at the edge of the smear, or be stacked on one another. The smear first should be examined under low power to assess adequacy of staining and cell distribution. The best place to search for properly spread erythrocytes is several millimeters inside the feathered edge of the smear. The erythrocytes should not be sprinkled with particulate matter from staining, and they should not be distorted from excessive water content in the stain. To assess erythrocyte morphology based on a blood smear that is poorly stained or spread is often futile and misleading. Erythrocyte shapes created by both artifact and disease include target cells, spherocytes, and stomatocytes. Artifactual spherocytes are especially common and can be distinguished from the true spherocyte by their size (they are larger than normal erythrocytes) and by the complete loss of central pallor in every cell, unlike in true spherocytes, in which central pallor still is present in many cells. Finally, when erythrocyte morphology is truly abnormal, the alterations in erythrocyte shape are apparent in different areas of the same smear and on different blood smears.

Blood-smear artifacts similarly can interfere with the evaluation of platelet and leukocyte morphology. Persistent platelet–leukocyte satellitism (resulting in spurious thrombocytopenia) may be observed on peripheral smears prepared from EDTA anticoagulated blood samples. Artifacts caused by delay in making the blood smear can adversely affect platelet and leukocyte morphology. Platelets become rounded and lose their granularity; granulocytes may lose toxic granulation and Döhle bodies, and their nuclei may become pyknotic. Cytoplasmic vacuolization also can increase. Thus, delay artifacts can obscure changes in granulocyte morphology associated with infection.

The blood smear can provide important information about erythrocyte abnormalities. In patients with severe hemolysis, examination of the blood smear for nucleated erythrocytes (sometimes accompanied by granulocytosis and thrombocytosis) and other characteristic erythrocyte shapes can be very useful; abnormalities include schistocytes and helmet cells (microangiopathic hemolytic anemia), spherocytes (immune mediated hemolytic anemia and hereditary spherocytosis), spiculated erythrocytes and acanthocytes (spur cells) in pyruvate kinase deficiency, and poikilocytosis and "bite" or "blister" cells in glucose-6-phosphate

dehydrogenase (G6PD) deficiency. Target cells are caused by alterations in the erythrocyte surface area, which, in dried smears, results in the outward bulge of excess membrane into the region of central pallor, creating the characteristic target appearance. Causes of targeting include iron deficiency, liver disease, hemoglobinopathies (hemoglobins C, D, and E), thalassemia, postsplenectomy state, hereditary xerocytosis, and lecithin–cholesterol acyl transferase deficiency. Howell-Jolly bodies are nuclear remnants that are not extruded from mature erythrocytes and indicate splenic hypofunction. Basophilic stippling caused by aggregated ribosomes in the erythrocyte (or ribosomal DNA and mitochodrial fragments in lead poisoning[7]) is seen with thalassemia and lead intoxication. Rouleaux formation occurs when plasma proteins block the negative charge on the erythrocyte surface, and red cells stack in long columns. Stacking occurs in several clinical conditions, especially when the erythrocyte sedimentation rate is elevated and is readily distinguishable from erythrocyte agglutination, in which erythrocyte aggregates are distorted and form clumps.

Leukocyte abnormalities similarly may indicate underlying pathology. Döhle bodies are bluish cytoplasmic inclusions that can be seen in the neutrophils from patients with bacterial infection, burns, myelodysplasia, the May-Hegglin anomaly, and in pregnancy. Coarse, dark granules are found in the neutrophils from patients with mucopolysaccharidosis and are referred to as *Alder-Reilly bodies*. In the Chédiak-Higashi syndrome, giant azurophilic granules are present in lymphocytes, whereas granulocytes contain very large irregular granules.

Hemoglobin and Hematocrit Values

Hemoglobin and hematocrit values relate to the number and content of erythrocytes, and when the measured hemoglobin is depressed, that is, more than two standard deviations below the mean, anemia exists. Several conditions may result in elevation of the hemoglobin or polycythemia. These conditions include primary (e.g., polycythemia vera) and secondary causes. Secondary causes of polycythemia include renal and posterior fossa brain tumors, cyanotic heart disease, and leftward shifts in the oxygen and hemoglobin dissociation curve caused by defects in synthesis of 2,3-diphosphoglycerate and from alterations in the hemoglobin molecule that increase its affinity for oxygen.[24, 49, 51, 52, 54] Infants with hematocrits exceeding 65% are at risk for a hyperviscosity syndrome that can be accompanied by hypoglycemia and central nervous system injury.[10]

EVALUATING ANEMIA: ROLE OF MCV, RDW, AND RETICULOCYTE COUNT

Approaches to the evaluation of anemia have been described extensively elsewhere, so this discussion focuses on components of the CBC

as a way to organize one's thinking about anemia. The MCV and the RDW provide a classification of erythrocytes based on their size and size distribution (Table 2).[9] In children, the MCV is less than in adults, and in children between the ages of 2 years and 10 years, the lower limit for MCV is approximately 70 fL + age (in years). The approximate upper limit for MCV is obtained by adding 0.6 fL per year to 84 fL beyond the first year of life until the upper limit of 96 fL in adults is reached.[23] Erythrocytes in children with anemia can be either small, large (↑ MCV), or normal in size, and in each size category, the RDW can be normal or increased (Table 2). The reticulocyte count, a measure of erythrocyte production, is also important in this evaluation. The reticulocyte count is expressed as the percentage of circulating erythrocytes. Reticulocytes are detected by their ability to take up reticulin stain, which reflects their increased RNA content. The normal range of the reticulocyte count is 0.5% to 1.5%, although the raw count is affected by the lifespan of the reticulocyte in circulation and by anemia. Therefore, the reticulocyte production index, which corrects for both anemia and reticulocyte maturation time, often is reported as a reliable measure of erythrocyte production with the following equation:

$$\text{RPI} = \frac{\%\ \text{reticulocytes}}{\text{reticulocyte maturation time (days)}} \times \frac{\text{hematocrit}}{\text{normal hematocrit}}$$

The normal reticulocyte lifespan is one day but lengthens inversely proportionately with the hematocrit and varies from one day when the hematocrit is normal to 2.5 days, when the hematocrit is 15%. Therefore,

Table 2. CLASSIFICATION OF ANEMIA BASED ON RED CELL MCV AND RDW

MCV Low		MCV Normal		MCV High	
RDW Normal	**RDW High**	**RDW Normal**	**RDW High**	**RDW Normal**	**RDW High**
Thalassemia trait	Iron deficiency	Normal	Mixed deficiency	Aplastic anemia	Folate deficiency
Chronic disease	S-β thalassemia	Chronic disease	Early iron or folate deficiency	Preleukemia	B_{12} deficiency
	Hemoglobin H	Sickle/Hb C trait	Hemoglobinopathy		Immune hemolysis
	Fragmentation	Hereditary spherocytosis	Myelofibrosis		Cold agglutinins
		Transfusion	Sideroblastic anemia		CLL*
		Chemotherapy CLL, CML			
		Hemorrhage			

*Caused by inclusion of leukocytes in the red cell volume distribution in CLL.

CLL, chronic lymphocytic leukemia; CML, chronic myelogenous leukemia; Hb, hemoglobin; MCV, mean corpuscular volume; RDW, red cell distribution width; S, sickle.

Data from Bessman JD, Gilmer PR Jr, Gardner FH: Improved classification of anemias by MCV and RDW. Am J Clin Pathol 80:322–326, 1983.

the double correction applied for the presence of polychromasia on the peripheral smear reflects the lengthened reticulocyte lifespan of 2 days.

Increased MCV

Patients with increased erythrocyte volume may be classified according to their corresponding reticulocyte count. In the patient with macrocytosis (↑MCV) and elevated reticulocyte count the cause of anemia often is caused by acute blood loss or hemolysis, a condition characterized by increased erythrocyte destruction. Ancillary measures of erythrocyte destruction—including serum bilirubin and lactate dehydrogenase (LDH), which are increased with hemolysis, and haptoglobin, which is decreased in intravascular hemolysis—can be useful in demonstrating accelerated erythrocyte destruction. In patients with hemolysis or blood loss, macrocytosis is caused by an increased number of reticulocytes, which have a large cellular volume (140–150 fL).

Anemia accompanied by macrocytosis in children frequently is caused by bone marrow failure. In patients with these syndromes, the reticulocyte count generally is diminished for the degree of anemia. The macrocytosis is caused by the production of 'stress' erythrocytes, which display fetal characteristics, including increased fetal hemoglobin content and expression of i antigen.[3] For changes caused by stress erythropoiesis to occur, at least some erythrocyte production is required, albeit at an insufficient rate. For this reason, in patients with severe aplastic anemia and pure red cell aplasia when erythropoiesis is absent, the resultant anemia may be normochromic and normocytic; however, stress erythropoiesis can be present in patients with these disorders with concomitant macrocytosis, making them difficult to distinguish from bone marrow failure syndromes like Fanconi's anemia and Diamond-Blackfan anemia (DBA). Drugs that interfere with erythropoiesis (e.g., valproate, zidovudine, and immunosuppressive agents) are a common cause of macrocytosis.[42]

Diamond-Blackfan anemia is a congenital hypoplastic anemia that most commonly presents in infancy, with 80% of cases occurring in the first 6 months of life.[2] This disorder usually is characterized by macrocytic anemia with reticulocytopenia, although many patients do not have an elevated MCV initially because of complete cessation of erythropoiesis. These patients become macrocytic, however, if some recovery of erythropoiesis occurs. White blood cell and platelet counts are generally normal, although the platelet count can be elevated.[13] Although most cases of DBA present before 1 year of age, as many as 5% of cases are identified later in life. For this reason, transient erythroblastopenia of childhood (TEC), which, in 90% of cases, occurs in children more than 1 year of age, can be confused with DBA.[53] TEC is a form of acquired red cell aplasia thought to be caused by viral or other toxic agents in which an immune reaction seems to occur against erythroid progenitor cells.[28] Some patients with TEC also may experience neutropenia.[46] Because

TEC is accompanied by cessation of erythropoiesis, the MCV is not increased initially; however, in the recovery phase of TEC, which is heralded by a marked reticulocytosis, the MCV is elevated. This recovery occurs within 1 to 2 months from the outset. Accordingly, expression of the i antigen and hemoglobin F production are low initially, increased during recovery from TEC (or following recovery from any marrow insult), and then return to normal following recovery. In addition, the erythrocyte adenosine deaminase level is increased in DBA (and other states of stress erythropoiesis) but is generally normal in patients with TEC.[29]

Other causes of macrocytic anemias are less common in childhood. The megaloblastic disorders, such as folate deficiency, vitamin B_{12} deficiency, and inherited disorders of DNA metabolism (e.g., inborn errors of folate metabolism), may be recognized by other alterations on the peripheral smear, including hypersegmentation of polymorphonuclear leukocytes and macroovalocytes. Examination of the bone marrow demonstrates megaloblastic changes that are diagnostic. Alcohol can cause a mild macrocytic anemia from a direct toxic effect on the bone marrow. Vacuolization of erythroid precursors may follow heavy ingestion of alcohol of just 1 week's duration.[35] Folic acid antimetabolites like methotrexate produce thrombocytopenia and leukopenia more often than megaloblastic changes. Other antimetabolites like trimethoprim are targeted at prokaryotic dihydrofolate reductase and have a low affinity for mammalian dihydrofolate reductase; however, they can cause acute folate deficiency when cellular levels of folate are already depressed. Hypothyroidism usually causes a normochromic, normocytic anemia caused by red cell hypoplasia, but macrocytosis may develop.

Decreased MCV

Microcytic anemias are caused by insufficient hemoglobin synthesis, resulting in hypochromia (cells with an enlarged region of central pallor), target shapes, and in more severe cases, markedly misshapened forms. In general, microcytosis is caused by iron deficiency or the inability to utilize iron, as occurs in anemia of chronic disease (discussed in detail elsewhere in this issue), thalassemia, lead poisoning, and sideroblastic anemia. Iron deficiency, as discussed later, is a common cause of microcytic anemia in children between 1 and 3 years of age. Some evidence shows that iron deficiency may potentiate the toxic effects of lead poisoning; in most cases, the anemia seen with lead poisoning is caused by iron deficiency and not lead toxicity so that testing for lead poisoning in endemic regions may be warranted in the child with documented iron deficiency.[18, 45]

Inherited disorders of hemoglobin synthesis also cause microcytic anemia. Children with β-thalassemia major present during the first 6 to 24 months of life with profound anemia, hepatosplenomegaly, jaundice, and growth retardation. β-thalassemia trait, the much more common

heterozygous state, may be confused with iron deficiency; however, some clues show that permit differentiation between them. First, the erythrocyte count is generally higher in the child with β-thalassemia trait, a characteristic on which the Mentzer index (MCV/red blood cell count [$\times 10^6$] < 12 in thalassemia trait and > 13 in iron deficiency) relies.[36] The blood smear also may be different, with a greater degree of poikilocytosis and basophilic stippling in the patient with thalassemia trait than with iron deficiency given the same level of anemia. In addition, the RDW is increased in the individual with iron deficiency and normal in β-thalassemia trait. Free erythrocyte protoporphyrin (FEP) also is elevated in iron deficiency but not in β-thalassemia trait. It is important to document that individuals suspected to have β-thalassemia trait must be iron replete prior to performing a diagnostic hemoglobin electrophoresis, because iron deficiency, which inhibits δ-globin chain synthesis, obscures the elevation of Hb A_2 in these individuals. α-Thalassemia trait (with two of the four α-globin genes deleted) typically causes microcytosis with or without a mild anemia, whereas hemoglobin H disease (deletion of three α-globin genes) results in microcytosis with a moderately severe hemolytic anemia. In these patients' erythrocytes, inclusion is seen following supravital staining with brilliant cresyl blue. The single α-globin gene deletion (silent carrier) usually causes neither microcytosis nor anemia but can be detected by hemoglobin electrophoresis in newborns when a small amount of Bart's hemoglobin (γ_4) can be detected.

Sideroblastic anemias, which are rare in childhood, are caused by failure to incorporate iron into heme, resulting in a microcytic anemia. The inherited form is usually X-linked. Acquired forms can occur in myelodysplastic syndromes, in which two populations of erythrocytes have been described (microcytes and normal or macrocytic erythrocytes). Other causes of acquired sideroblastic anemia include isoniazid, ethanol, and other drugs. The diagnosis of sideroblastic anemia is confirmed by demonstrating ringed sideroblasts on iron staining of the bone marrow. The presence of Pappenheimer bodies (iron-laden mitochondria) in erythrocytes on the peripheral blood smear similarly support this diagnosis, although they also can be demonstrated in the postsplenectomy state.

Anemia with a Normal MCV

Normocytic anemia with an elevated reticulocyte count often is caused by hemolysis or blood loss; however, patients with hemolysis are not necessarily anemic if increased erythropoiesis is adequate to compensate for the shortened erythrocyte life span. Other causes of normocytic anemia include balanced causes of macrocytic and microcytic anemia, such as iron deficiency combined with folate or B_{12} deficiency. In these uncommon situations, it is important to distinguish between erythrocytes of normal size versus a mixture of small and large

erythrocytes creating a "normal" MCV. In the latter case, the RDW is increased greatly, reflective of erythrocyte populations of different sizes.

Causes of normocytic anemia that were discussed earlier include acquired pure red cell aplasia (TEC), aplastic anemia, and hypothyroidism, although these conditions also are often accompanied by macrocytic erythrocytes. In addition, replacement of the marrow space by malignant cells in myelophthisis may cause normocytic anemia. Malignant cells may originate in the marrow, as occurs with leukemia, lymphoma, and the histiocytoses, or may be metastatic from primary solid tumor origins, as in neuroblastoma, Ewing's sarcoma, and medulloblastoma. Storage diseases in an advanced stage similarly can replace the marrow space.

Normocytic and normochromic anemias associated with a normal or low reticulocyte count and with a normal RDW should alert one to the possibility of a chronic infection or a chronic inflammatory process (see article by Abshire elsewhere in this issue). Moreover, the anemias of renal and liver disease are normocytic. Anemias of renal disease are primarily the result of erythropoietin insufficiency,[11] although serum inhibitors of erythropoiesis may accumulate in the uremic patients, and hyperparathyroidism may inhibit erythropoiesis by promoting fibrosis in the marrow cavity.[14, 31] With blood urea nitrogen concentrations more than 150 mg/dL, acanthocytosis may develop, and erythrocyte life span is shortened.[1] The anemia of liver disease is multifactorial and includes hypersplenism, concomitant vitamin-nutritional deficiencies, and blood loss. The characteristic spur cell in liver disease, which is caused by an alteration in lipid composition of the membrane,[19] is often a late and ominous development.

Mean Corpuscular Hemoglobin Concentration

The MCHC is most useful as a method for detecting erythrocyte cellular dehydration. Hereditary spherocytosis is a hemolytic anemia caused by a membrane defect. The MCHC of hereditary spherocytosis erythrocytes is increased above the upper limit of normal (36 mg/dL) in approximately 50% of cases, but most patients have some erythrocytes that are dehydrated.[34] Patients with sickle cell anemia also may have populations of erythrocytes with elevated hemoglobin concentration because of cellular dehydration. These populations of cells are not readily detected by the Coulter electric impedance instrument but can be seen with instruments that rely on light scatter methodology to measure erythrocyte indices (Technicon*H1, Technicon Instruments, Tarrytown, NY). This methodology provides the advantage of measuring MCHC directly and thus bypasses difficulties with poor cellular deformability encountered when calculating MCHC by electric impedance in erythrocytes with MCHC above 36 g/dL.[38] It is particularly useful in assisting with the diagnosis of hereditary spherocytosis by documenting in a histogram the presence of a characteristic population of cells with an elevated MCHC.

NEWBORN INFANTS

CBC determinations frequently are obtained in the newborn period, often as part of an evaluation of infection, jaundice, or pallor. For interpretation of the hemoglobin value in the neonate, the method of its collection becomes an important consideration.[37] Blood samples can be obtained from a central site, via either venepuncture, a central indwelling catheter (e.g., umbilical artery/vein), or pricking the skin of an extremity for collection of capillary blood. Blood samples collected from central sites are generally most reliable for hemoglobin determination; alternatively, capillary blood samples are much less reliable, with a tendency for capillary blood to overestimate the actual central hemoglobin.[39] This occurs despite a higher plasma content in smaller blood vessels (i.e., capillaries) and a somewhat larger erythrocyte volume among oxygen-carrying red cells in capillary blood. In fact, the ratio of hemoglobin values from capillary and central sites can be as high as 1.2:1, with the greatest disparity occurring in infants who are most ill (e.g., premature infants and neonates with hypotension, acidosis, or marked anemia[32]).

Normal values for hemoglobin/hematocrit for term and preterm infants are presented in Table 3. Although premature infants tend to have lower hemoglobin values because of the shorter period for hemoglobin synthesis in utero, the differences largely disappear after 32 to 33 weeks' gestation.[27] The erythrocyte size is increased in premature infants because of the relative abundance of larger fetal erythrocytes. The MCV at birth declines continuously with gestational age, which coincides with the switch from γ to β-globin chain synthesis, as does the reticulocyte count (Table 3).

Anemia in the newborn frequently is caused by blood loss. Sources of blood loss include placental transfusion, in which an infant may lose 10% to 20% of his or her blood volume if positioned above the placenta for too long), fetal-maternal hemorrhage, umbilical cord hemorrhage, twin-twin hemorrhage, and internal hemorrhage. Other causes of anemia to consider in newborns include disorders of erythrocyte production and maturation (e.g., Diamond-Blackfan anemia) and hemolysis caused by isoimmune or infectious processes, hereditary disorders of hemoglobin and its production, and disorders of the erythrocyte membrane (e.g., hereditary spherocytosis) or metabolism (e.g., G6PD deficiency).

Once anemia caused by blood loss has been diagnosed in neonates, differentiation between chronic and acute blood loss is likely to have an impact on management. Neonates with acute blood loss have erythrocytes with normal MCV and MCH for age and may have a normal hemoglobin initially that then declines precipitously in the first 24 hours of life[40] (Table 4). Clinically, these infants are generally in distress, with pallor, tachypnea, tachycardia, and hypotension. The physical examination usually reveals no hepatosplenomegaly. These infants require resuscitation with volume-expanding intravenous solutions and whole blood.

Table 3. RED CELL VALUES ON THE FIRST POSTNATAL DAY

	Gestational Age (weeks)							
Measurement	**24–25**	**26–27**	**28–29**	**30–31**	**32–33**	**34–35**	**36–37**	**Term**
RBC × 10^6	4.65 ± 0.43	4.73 ± 0.45	4.62 ± 0.75	4.79 ± 0.74	5.0 ± 0.76	5.09 ± 0.5	5.27 ± 0.68	5.14 ± 0.7
Hb (g/dL)	19.4 ± 1.5	19.0 ± 2.5	19.3 ± 1.8	19.1 ± 2.2	18.5 ± 2.0	19.6 ± 2.1	19.2 ± 1.7	19.3 ± 2.2
Hct (%)	63 ± 4	62 ± 8	60 ± 7	60 ± 8	60 ± 8	61 ± 7	64 ± 7	61 ± 7.4
MCV (μ^3)	135 ± 0.2	132 ± 14.4	131 ± 13.5	127 ± 12.7	123 ± 15.7	122 ± 10.0	121 ± 12.5	119 ± 9.4
Retics (%)	6.0 ± 0.5	9.6 ± 3.2	7.5 ± 2.5	5.8 ± 2.0	5.0 ± 1.9	3.9 ± 1.6	4.2 ± 1.8	3.2 ± 1.4
Weight (g)	725 ± 185	993 ± 194	1174 ± 128	1450 ± 232	1816 ± 192	1957 ± 291	2245 ± 213	

From Zalzov R, Matoth Y: Red cell values on the first postnatal day during the last 16 weeks of gestation. Am J Hematol 1:276, © 1976; reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

Table 4. CHARACTERISTICS OF ACUTE AND CHRONIC BLOOD LOSS IN NEWBORNS

Characteristics	Acute Blood Loss	Chronic Blood Loss
Clinical features	Acute distress; pallor; shallow, rapid, and often irregular respiration; tachycardia; weak or absent peripheral pulses; low or absent blood pressure; no hepatosplenomegaly	Marked pallor disproportionate to evidence of distress; on occasion signs of congestive heart failure, including hepatomegaly
Venous pressure	Low	Normal or elevated
Laboratory values		
Hemoglobin concentration	May be normal initially; then drops quickly during first 24 hours of life	Low at birth
Red cell morphology	Normochromic and macrocytic	Hypochromic and microcytic; anisocytosis and poikilocytosis
Serum iron	Normal at birth	Low at birth
Course	Prompt treatment of anemia and shock necessary to prevent death	Generally uneventful
Treatment	Intravenous fluids and whole blood; iron therapy later	Iron therapy; packed red cells may be necessary on occasion

From Oski FA: The erythrocyte and its disorders. *In* Nathan DG, Oski FA (eds): Hematology of Infancy and Childhood, ed 4. Philadelphia, WB Saunders, 1993, p 31.

Following stabilization, they need iron-replacement therapy in excess of that provided to normal neonates.

Neonates with chronic anemia caused by blood loss demonstrate a lowered hemoglobin concentration with a depressed MCV. A peripheral blood smear shows hypochromic, microcytic erythrocytes. Clinically, these infants are generally without distress, although occasionally they demonstrate hepatosplenomegaly and signs of congestive heart failure. These infants do not routinely require acute intervention, and a transfusion of red cells rarely is necessary. Iron replacement therapy clearly is indicated for these infants.

Physiologic Anemia of Infancy

At birth, the increased oxygen tension following conversion from maternal to environmental oxygenation results in a rapid decline in erythropoiesis, as shown by reductions in reticulocyte count, hemoglobin, and erythroid progenitors in the bone marrow. Eventually, as the

hemoglobin–oxygen dissociation curve becomes progressively right-shifted, resulting from conversion of fetal to adult hemoglobin and as the hemoglobin level falls, a threshold of diminishing venous oxygen saturation is reached. A signal in the form of increased erythropoietin production is sent to the marrow, and erythropoiesis is stimulated, eventually resulting in a rising hemoglobin value. This fall in hemoglobin production together with the shortened life span of fetal erythrocytes creates a physiologic hemoglobin nadir at 7 to 10 weeks of age in normal newborns (Table 5). Agents that either impair erythrocyte production or decrease red cell survival (e.g., infection, medications, or hemolysis) can lead to an earlier or lower nadir. This is commonly encountered in premature infants.[22] Because of their smaller red cell mass, premature infants reach their nadir earlier than term infants and require a longer period of time to recover, in part because of an impaired erythropoietin response to tissue hypoxemia[47, 48] (Fig. 3). Hemoglobin levels begin to fall by the end of the first week of life and may take as many as 4 months to recover. Because of this blunted response, premature infants will more likely develop symptoms related to inadequate tissue oxygen delivery and require transfusion of red cells or recombinant eythropoietin therapy.

Table 5. NORMAL RED CELL VALUES DURING THE FIRST 12 WEEKS OF LIFE

Age	*n*	Hb (g/dL) ± 1 SD	Hct (%) ± 1 SD	MCV (μ^3) ± 1 SD	Retic (%) ± 1 SD
Days					
1	19	19.0 ± 2.2	61 ± 7.4	119 ± 9.4	3.2 ± 1.4
2	19	19.0 ± 1.9	60 ± 6.4	115 ± 7.0	3.2 ± 1.3
3	19	18.7 ± 3.4	62 ± 9.3	116 ± 5.3	2.8 ± 1.7
4	10	18.6 ± 2.1	57 ± 8.1	114 ± 7.5	1.8 ± 1.1
5	12	17.6 ± 1.1	57 ± 7.3	114 ± 8.9	1.2 ± 0.2
6	15	17.4 ± 2.2	54 ± 7.2	113 ± 10.0	0.6 ± 0.2
7	12	17.9 ± 2.5	56 ± 9.4	118 ± 11.2	0.5 ± 0.4
Weeks					
1–2	32	17.3 ± 2.3	54 ± 8.3	112 ± 19.0	0.5 ± 0.3
2–3	11	15.6 ± 2.6	46 ± 7.3	111 ± 8.2	0.8 ± 0.6
3–4	17	14.2 ± 2.1	43 ± 5.7	105 ± 7.5	0.6 ± 0.3
4–5	15	12.7 ± 1.6	36 ± 4.8	101 ± 8.1	0.9 ± 0.8
5–6	10	11.9 ± 1.5	36 ± 6.2	102 ± 10.2	1.0 ± 0.7
6–7	10	12.0 ± 1.5	36 ± 4.8	105 ± 12.0	1.2 ± 0.7
7–8	17	11.1 ± 1.1	33 ± 3.7	100 ± 13.0	1.5 ± 0.7
8–9	13	10.7 ± 0.9	31 ± 2.5	93 ± 12.0	1.8 ± 1.0
9–10	12	11.2 ± 0.9	32 ± 2.7	91 ± 9.3	1.2 ± 0.6
10–11	11	11.4 ± 0.9	34 ± 2.1	91 ± 7.7	1.2 ± 0.7
11–12	13	11.3 ± 0.9	33 ± 3.3	88 ± 7.9	0.7 ± 0.3

Hb, hemoglobin; MCV, mean corpuscular volume; *n*, number of cases; Retic, reticulocytes; SD, standard deviation.

From Matoth, Y, Zalzov R, et al: Postnatal changes in some red cell parameters. Acta Paediatr Scand 60:317, 1971; with permission.

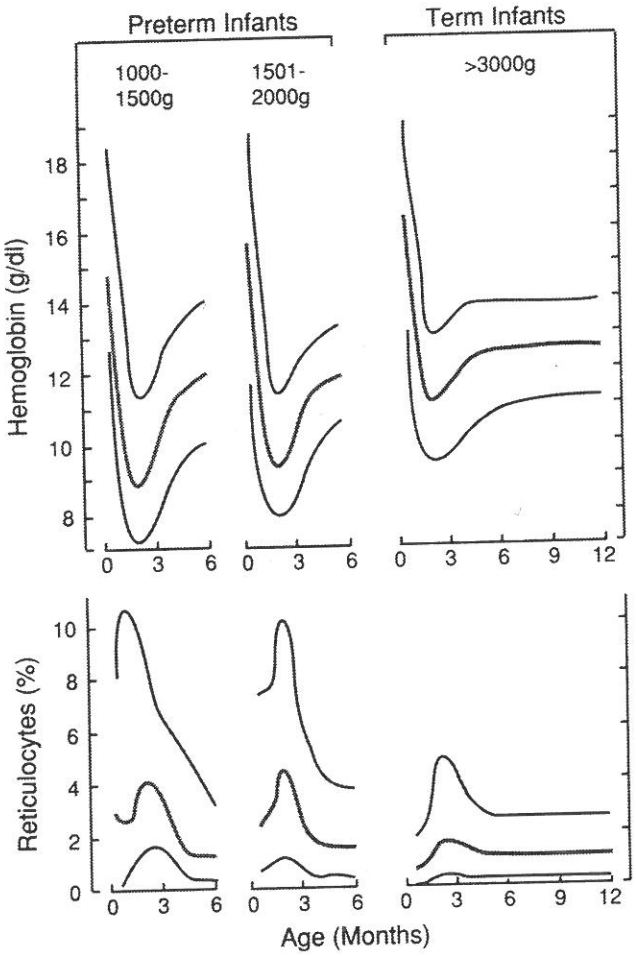

Figure 3. Physiologic nadir for term and preterm infants. The mean and range of normal hemoglobin and reticulocyte values for term and preterm infants are shown. Premature infants reach a nadir of erythrocyte production sooner and require longer to recover than their term infant counterparts. (*From* Dallman PR: Anemia of prematurity. Ann Rev Med 32:143, 1981; reproduced, with permission, from the Annual Review of Medicine, volume 32, © 1981, by Annual Reviews, Inc.)

Screening Hemoglobin at 9 to 12 Months of Age: Iron Deficiency

Collecting a hemoglobin and hematocrit value at 9 to 12 months of age to screen for anemia is a common practice among pediatricians. The most common causes of anemia in this age group are iron deficiency and, as discussed elsewhere in this issue, intercurrent infection.[41] Today, more infants are breast-fed or receive iron-fortified formula, and fewer

receive large amounts of cow's milk during the first year of life, thus contributing to a lower incidence of severe iron deficiency among infants in the United States than in prior decades[57]; however, iron deficiency persists as a substantial public health problem.[44] Anemia caused by iron deficiency is a late step in the pathophysiology of iron deficiency. First, as iron stores become depleted, the serum ferritin concentration declines and the RDW increases. Next, serum iron concentration becomes depressed. Finally, iron deficiency begins to affect erythropoiesis, causing a decrease in the MCV and an increase in the free erythrocyte protoporphyrin with accompanying anemia.

The first hematologic manifestation of iron deficiency is increase in the RDW (normal range in children, 11.5% to 14.5%). This alteration may be more sensitive in screening for iron deficiency than serum ferritin, transferrin saturation, or even serum iron level, some of which can be altered by inflammation or even variation in iron intake.[43] Moreover, the increased RDW may be useful in discriminating microcytosis secondary to iron deficiency from thalassemia trait, in which the RDW is normal.[8] The hematologic values indicative of iron deficiency and cutoff values used by the Second National Health and Nutrition Examination Survey and the values recognized by the American Academy of Pediatrics are shown in Table 6.[17, 56]

Although rigorous testing may be required to be secure about the cause of anemia in the 9-month to 12-month hemoglobin screen, a reasonable approach in this cost-conscious era has been a trial of oral iron replacement for children whose hemoglobin levels fall below the 10th percentile. Thus, in patients with anemia accompanied by an increased RDW and a supportive history who respond to a trial of iron (defined as an increase of 1.5–2.0 g/dL in the hemoglobin after 1 month of therapy), a presumptive diagnosis of iron deficiency anemia usually can be made.

Although iron deficiency is common in children 9 months to 3 years of age and in teenage girls, it is unusual in other children. Thus iron deficiency anemia in children more than 3 years of age generally should prompt consideration of occult blood loss. Infants fewer than 6 months of age generally do not develop iron deficiency provided iron stores accumulated during intrauterine life were adequate and they have not been fed cow's milk, which frequently causes occult intestinal blood loss at this age. The exception to this rule is premature infants, who are at risk for developing iron deficiency as early as 4 months of age if iron supplementation is not provided.

PLATELETS

Alterations in platelet numbers and platelet size can provide important clues to disease processes. Platelet size is most often determined from review of the peripheral smear, but mean platelet volume also can be derived by the Coulter counter. Platelets are normally 1 to 4 μ^3–

Table 6. COMMON LABORATORY TESTS AND CUTOFF VALUES FOR THE DIAGNOSIS OF IRON DEFICIENCY IN CHILDREN*

Test	Age (yr)	Cutoff Value	
Biochemical			
Serum iron	1–2	<30 μg/dl (5.4 μmol/liter)	
	3–5	<30 μg/dl	
Total iron-binding capacity	1–3	>480 μg/dl (86.0 μmol/liter)	
	3–5	>470 μg/dl (84.2 μmol/liter)	
Transferrin saturation	1–2	<8%	
	3–5	<9%	
Erythrocyte protoporphyrin	1–5	≥35 μg/dl of whole blood (0.62 μmol/liter), ≥90 μg/dl of red cells (1.6 μmol/liter), ≥3.0 μg/g of hemoglobin, or ≥90 μmol/mol of heme	
Serum ferritin	1–5	8 to 12 μg/liter	
		NHANES II	**AAP**
Hematologic			
Hemoglobin	1–2	<10.7 g/dl	<11.0 g/dl
	3–5	<10.9 g/dl	<11.0 g/dl
Hematocrit	1–2	<32%	<33%
	3–5	<32%	<34%
Mean corpuscular volume	1–2	<67μm³	<70 μm³
	3–5	<73 μm³	<73 μm³
Mean corpuscular hemoglobin	1–2	<22pg	—
	3–5	<25 pg	—
Mean corpuscular hemoglobin concentration	1–2	<32 g/dl	—
	3–5	<32 g/dl	—
Red/cell distribution width†	1–5	>14.5%	

*NHANES II denotes the Second National Health and Nutrition Examination Survey, and AAP the Committee on Nutrition of the American Academy of Pediatrics.
†Not included in the NHANES II or AAP guidelines.

diameter cytoplasmic fragments with red-purple granules and no nucleus. In general, platelets tend to be larger when there is peripheral destruction, e.g., immune mediated or on a mechanical basis, and normal to small in size when production defects are present. In Wiskott-Aldrich syndrome, platelets are about half of normal size and look like dust particles. Large platelets are generally thought to be young, which in part may be true, but increased mean platelet volume and large platelets also may be a reflection of stimulated thrombopoiesis. The normal life span of platelets is 7 to 10 days. Approximately one third of the body's platelets are located in the spleen and two thirds in the circulation.

Practitioners most often are interested in whether too few or too many platelets are present and whether they work properly. The CBC cannot answer functional questions, but the significance of thrombocytopenia and thrombocytosis can be clarified. There is a wide range of normal platelet counts, but thrombocytopenia generally is defined as a platelet count of fewer than 150,000/mm³ and thrombocytosis as values between 600,000/mm³ and 1,000,000/mm³ or more.

Thrombocytosis

Thrombocytosis in childhood rarely causes complications, although it is frequently a concern. Primary causes of thrombocytosis, such as polycythemia vera and essential thrombocythemia, are unusual in childhood and may have a more favorable outcome than in older individuals.[30] Elevated platelet counts in childhood almost always are reactive, relating to underlying conditions. Infections are the most common cause, but the differential diagnosis includes several other entities, such as iron deficiency anemia, hemolytic anemia, vitamin E deficiency, hemorrhage, collagen vascular disorders, Kawasaki syndrome (usually 2–3 weeks into the illness), nephrotic syndrome, inflammatory bowel disease, following splenectomy, postoperative state, trauma, various tumors, myeloproliferative syndromes, histiocytoses, and various drugs, such as epinephrine, corticosteroids, and vinca alkaloids.[15] Because no apparent sequelae exist to reactive thrombocytosis, antiplatelet therapy is rarely indicated (Kawasaki syndrome is a notable exception). Platelet morphology is usually normal, as is the bleeding time. Splenomegaly is absent unless caused by the underlying disorder, and the duration is transitory, usually measured in days to weeks.

Thrombocytopenia

When thrombocytopenia is reported, the most common cause is immune platelet destruction, but falsely low platelet counts may occur when inadequate anticoagulation of the blood-sample results in platelet clumping. The precision of platelet counting by automated instruments is reduced in the severe thrombocytopenia range (platelets fewer than 20,000/mm³) because loss of measurement linearity occurs.

Thrombocytopenia is associated with a wide range of infections and other conditions. The major issues confronting practitioners are the risk of life-threatening bleeding and the possibility of a serious underlying condition. Isolated thrombocytopenia without other hematologic abnormalities in an otherwise healthy appearing child without lymphadenopathy or hepatosplenomegaly almost never is associated with childhood acute leukemia. In such cases, idiopathic thrombocytopenic purpura (ITP) is usually the correct diagnosis. As described more fully elsewhere in this issue, intracranial hemorrhage occurs only rarely in children with ITP.[55]

WHITE BLOOD CELLS

The total and differential white blood cell count often can be a clue to underlying disorders. It is also true that the white blood cell count is sometimes requested without much thought. Its usefulness as a screening test is not great because both sensitivity and specificity are low; however, the reliability and low cost of

justifies these tests as part of the complete blood count, although abnormalities and definitive characterizations still require examination of the peripheral smear.

Practitioners generally are interested in the total and differential white blood cell count as clues to underlying infection. Interpretation of white count numbers is aided by the clinical context, for example, the age of the patient, temperature, general appearance, and underlying conditions. Although the white blood cell response to infection can be highly variable, the younger the patient and the higher the temperature, the more one becomes suspicious if the white blood cell count is either above or below the normal range (Table 7).

Leukopenia is associated with a wide variety of viral and bacterial infections. When caused by a viral illness (e.g., Epstein-Barr virus, hepatitis A and B, respiratory syncytial virus, and rubella), acute changes usually are noted within 1 to 2 days of infection and often can persist for several weeks. If the clinical situation warrants, consideration should be given to salmonella, staphylococcal, and mycobacterial infections. Neutropenia (neutrophil count $< 1500/mm^3$) most often is associated with viral infections and often is discovered as an incidental finding.

Leukocytosis is part of the body's acute phase response to many conditions, including infections. Bacteria, virus, fungi, protozoa, and spirochetes all can cause leukocytosis. We are often left with the perplexing situation of determining which febrile child with leukocytosis requires additional diagnostic studies or treatment. As noted earlier, the practitioner's skill and experience are critical in making a determination. In children 3 to 36 months of age with fever 39.5°C or more, bacteremia is highly correlated with white blood cell count. In one study, total white blood cell count of more than 15,000 cells/mm^3 was associated with 16% incidence of bacteremia, above 20,000 cells/mm^3 there was a 25% incidence, and more than 30,000 cells/mm^3 the incidence was closer to 40%.[5] The overall approach to the management of febrile children without an obvious source of infection has stirred considerable discussion.[4, 26, 33]

Attention should also be paid to the band count. When appreciable numbers of bands and more immature forms are present in the peripheral blood, it is generally referred to as a "left shift." Instead of using this term, considering the absolute number of band forms may be more useful. Beyond the neonatal period, more than 500 bands/mm^3 is an indication of infection regardless of the absolute white blood cell count. Although an increase in band forms classically has been thought to be associated with bacterial infections, a recent study of children with proven viral infections (e.g., influenza, enterovirus, respiratory syncytial virus, and rotavirus) showed significant elevations in absolute numbers of band forms.[50] Further, if toxic granules (larger than normal granules that stain intensely), vacuolization, or Döhle bodies are reported on the peripheral smear, possible bacterial infection also should be suspected. In the end, no substitute exists for astute clinical judgment coupled with judicious interpretation of laboratory tests, especially when trying to differentiate a viral from bacterial process.

Table 7. NORMAL LEUKOCYTE COUNTS*

Age	Total Leukocytes		Neutrophils			Lymphocytes			Monocytes		Eosinophils	
	Mean	Range	Mean	Range	%	Mean	Range	%	Mean	%	Mean	%
Birth	18.1	9.0–30.0	11.0	6.0–26.0	61	5.5	2.0–11.0	31	1.1	6	0.4	2
12 h	22.8	13.0–38.0	15.5	6.0–28.0	68	5.5	2.0–11.0	24	1.2	5	0.5	2
24 h	18.9	9.4–34.0	11.5	5.0–21.0	61	5.8	2.0–11.5	31	1.1	6	0.5	2
1 wk	12.2	5.0–21.0	5.5	1.5–10.0	45	5.0	2.0–17.0	41	1.1	9	0.5	4
2 wk	11.4	5.0–20.0	4.5	1.0–9.5	40	5.5	2.0–17.0	48	1.0	9	0.4	3
1 mo	10.8	5.0–19.5	3.8	1.0–9.0	35	6.0	2.5–16.5	56	0.7	7	0.3	3
6 mo	11.9	6.0–17.5	3.8	1.0–8.5	32	7.3	4.0–13.5	61	0.6	5	0.3	3
1 y	11.4	6.0–17.5	3.5	1.5–8.5	31	7.0	4.0–10.5	61	0.6	5	0.3	3
2 y	10.6	6.0–17.0	3.5	1.5–8.5	33	6.3	3.0–9.5	59	0.5	5	0.3	3
4 y	9.1	5.5–15.5	3.8	1.5–8.5	42	4.5	2.0–8.0	50	0.5	5	0.3	3
6 y	8.5	5.0–14.5	4.3	1.5–8.0	51	3.5	1.5–7.0	42	0.4	5	0.2	3
8 y	8.3	4.5–13.5	4.4	1.5–8.0	53	3.3	1.5–6.8	39	0.4	4	0.2	2
10 y	8.1	4.5–13.5	4.4	1.8–8.0	54	3.1	1.5–6.5	38	0.4	4	0.2	2
16 y	7.8	4.5–13.0	4.4	1.8–8.0	57	2.8	1.2–5.2	35	0.4	5	0.2	3
21 y	7.4	4.5–11.0	4.4	1.8–7.7	59	2.5	1.0–4.8	34	0.3	4	0.2	3

*Numbers of leukocytes are in thousands per μL; ranges are estimates of 95% confidence limits; percentages refer to differential counts. Neutrophils include band cells at all ages and a small number of metamyelocytes and myelocytes in the first few days of life.

From Dallman PR: *In* Rudolph AM (ed): Pediatrics, ed 16. New York, Appleton-Century-Crofts, 1977, p 1178; with permission.

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Eosinophilia often is associated with rashes, wheezes, and unusual diseases. Common examples of unusual diseases are parasitic infections; in the United States, they are most often visceral larva migrans. Eosinophilia also is associated with drug hypersensitivity, asthma, cow's milk allergy, hay fever, urticaria, eczema, other skin disorders, Job's syndrome, and malignancy.

Lymphocytosis most often is associated with viral infections, including infectious mononucleosis, cytomegalovirus, rubella, mumps, and hepatitis. White blood cell counts of more than 30,000/mm^3 with 60% to 70% lymphocytes, especially if they are described as clefted or "baby bottom," may be caused by pertussis.

Distinguishing leukemoid from leukoerythroblastic reactions is important. In leukoerythroblastic reactions, nucleated red blood cells and immature white blood cells are found in a setting of underlying leukemia, myelophthisis, severe bleeding, or hemolysis. Leukemoid reactions, on the other hand, are elevations in the white blood cell count, in excess of 50,000/mm^3, sometimes leading to confusion with leukemia. There are many causes of leukemoid reactions, which can be either myeloid or lymphoid.

SUMMARY

The authors' impression is that the CBC provides much more information than is routinely used. When anemia is present, the CBC contains considerable information regarding its cause, which can assist in formulating a differential diagnosis and directing further evaluation. White blood cell and platelet count levels may similarly direct practitioners to consider or dismiss underlying conditions. This article assists the pediatrician in optimizing use of this familiar diagnostic tool.

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