The Complete Blood Count: A Practical Tool for the Pediatrician

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PRACTICE GAPS

Interpretation of the complete blood count (CBC) is not a simple task. Laboratory reports include a variety of useful values that may be overlooked. It is important for all practitioners to develop an adequate foundation in CBC interpretation early in their career. Possessing a thorough understanding of the results reported in the CBC allows the practitioner to focus subsequent evaluation and reduce unnecessary laboratory testing.

OBJECTIVES *After completing this article, readers should be able to:*

1. Apply basic concepts of complete blood count (CBC) interpretation in pediatrics.
2. Locate the normal range for CBC for pediatric patients and understand how values may be affected by age and sex.
3. Use an algorithm for CBC interpretation.
4. Recognize the most common blood disorders identified on the CBC.
5. Narrow a differential diagnosis based on specific values in the CBC.

ABSTRACT

Every child should have a baseline hematology evaluation with hemoglobin and hematocrit levels starting at age 12 months, or younger if clinically indicated. Although history and physical examination provide key information needed to diagnose blood disorders, the addition of a complete blood count (CBC) with differential count and reticulocyte count allows the clinician to narrow the differential diagnosis and tailor the subsequent evaluation. The interpretation of CBC results is a skill that requires practice. Every clinician can learn to identify possible diagnoses before consulting a specialist. This review provides a step-by-step approach for CBC interpretation with tools to help the clinician diagnose and interpret the most common blood disorders seen in the general pediatric clinic or inpatient setting.

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ABBREVIATIONS

AEC	absolute eosinophil count
ANC	absolute neutrophil count
CBC	complete blood count
Hgb	hemoglobin
Hct	hematocrit
MCV	mean corpuscular volume
MCHC	mean corpuscular hemoglobin concentration
RBC	red blood cell
RDW	red blood cell distribution width
WBC	white blood cell

COMPLETE BLOOD COUNT

The CBC is one of the most commonly ordered laboratory tests. The ability to measure the number of blood cells was made possible by the development of a cell counter by Wallace H. Coulter, a technological innovator in the field of modern hematology. (1) Modern Coulter counters have been modified to offer many blood values that can be used to guide the diagnosis and treatment of blood disorders.

The interpretation of CBC results should be carefully guided by a good history and physical examination. The American Academy of Pediatrics recommends screening for anemia between ages 9 and 12 months, with additional screening between ages 1 and 5 years for patients at risk. (2) One reason for this recommendation is the early detection of iron deficiency anemia, the most common cause of anemia worldwide. In addition, a screening CBC may help identify patients earlier with underlying blood disorders, allowing for more timely treatment initiation or referral.

The CBC is an extremely useful laboratory tool allowing measurement of red blood cells (RBCs), white blood cells (WBCs), and platelets. These results should be interpreted using other values reported in the CBC, such as RBC indices, differential cell count, and platelet size. The CBC can be ordered as a routine examination to diagnose medical conditions in the setting of clinical symptoms and to monitor progression or improvement of a medical condition or treatment response over time. Although automatic hematologic analyzers are commonly used to perform a CBC, manual hematology evaluation, such as a peripheral blood smear review, is often necessary in the diagnosis of blood disorders. This technique includes cell separation by centrifugation and counting on the hemocytometer (slides with counting grid) under the microscope by laboratory technicians. (3)

The ability to differentiate between normal and abnormal requires the development of reference ranges for laboratory results. Some values vary depending on age (newborn hemoglobin [Hgb] values are much higher than infant or toddler values) and, therefore, require age-based interpretation. After puberty, CBC begin to show sex differences (male Hgb values are higher than female Hgb values). Historically, race and ethnicity have been thought to produce different reference ranges for Hgb levels, WBC counts, and neutrophil counts. This may be attributed to the use of reference ranges that represent a homogenous white population and are not multiethnic or multiracial in their representation as well as the presence of health-care disparities, which may result in a higher prevalence of disease in minority populations. (4) In general, there is a movement toward eliminating the use of race-based reference ranges, although many textbooks still include race-based tables. Therefore, this review attempts to point out CBC results that have been attributed to race to raise clinician awareness but uses reference tables that are not race-based. Understanding variation and limitation in reference ranges make the CBC a more useful tool.

This article has been divided into 3 major sections: RBCs, WBCs, and platelets. In addition, evaluation algorithms are provided to allow for rapid assessment and are divided based on cell type. The complete clinical interpretation of the CBC requires that all results also be reviewed together as some conditions may affect more than 1 cell type. (5) These algorithms should not replace clinical judgment and will be limited to the most common blood disorders. It is highly recommended to refer the patient for further evaluation with a subspecialist if a blood disorder is suspected.

RED BLOOD CELLS

RBCs, or erythrocytes, are a unique cell type because they extrude their nucleus while in the marrow at maturation and circulate without a nucleus in the peripheral blood. Adult RBCs have an average life span of 120 days in the bloodstream and are produced daily under normal conditions in the bone marrow. (6) The RBC is rich with Hgb, which is responsible for gas exchange and oxygen delivery to the tissues. Drastic changes in blood volume directly affect the normal function and oxygen delivery of the RBC.

The CBC offers descriptive information about the RBC. Specific measurements of the RBC allow the characterization of blood disorders based on RBC indices such as the RBC distribution width (RDW), mean corpuscular volume (MCV), RBC count, mean corpuscular hemoglobin level, or mean corpuscular hemoglobin concentration (MCHC). To fully evaluate the clinical impact of various RBC indices, clinicians should establish a systematic approach to evaluating the CBC, applying this approach consistently in conjunction with the clinical scenario. One useful approach involves using the MCV to divide types of anemia based on RBC size. In this review, we divide RBC algorithms into 3 major groups: microcytic anemia (<2.5th percentile for age, sex), normocytic anemia (2.5th–97.5th percentile for age, sex), and macrocytic anemia (>97.5th percentile for age, sex).

RBC indices can help distinguish between pathologic and nonpathologic disorders. Most patients who have abnormal values associated with a pathologic disorder will have signs and symptoms that help guide the development

of a differential diagnosis. Patients with anemias can have a broad clinical presentation based on the severity and onset of presentation. Acute anemias tend to be more symptomatic than chronic anemias in which physiologic changes occur slowly, thereby diminishing the immediate severity of signs and symptoms as the chronic anemia develops. Patients with an acute drop in Hgb may present with extreme changes in vital signs, such as tachycardia, as well as other signs and symptoms, such as headache, fatigue, shortness of breath, pallor, weakness, and/or lightheadedness. For patients with acute symptom onset, one should consider blood loss or hemolysis as the major cause. Chronic anemia tends to have a more indolent course, making the history and physical examination necessary for the correct diagnosis.

The goal of this review is to provide a basic tool for clinicians to maximize the utility of CBC results in the identification of the most common pathologies. It is beyond the scope of this review to discuss every diagnosis in detail. The classic definition of anemia may not apply to all patient populations, such as patients with underlying hypoxia due to conditions that include congenital heart disease, chronic respiratory disorders, or arteriovenous pulmonary shunts. Patients with cyanotic conditions will have higher baseline Hgb values due to hypoxia, which is necessary to provide appropriate tissue oxygenation. (7) Patients with hypoxic disorders may seem to have values that are normal for their age based on reference ranges but really represent anemia compared with their personal baseline.

A special consideration when evaluating a CBC is the presence of nucleated RBCs on the peripheral blood smear. Nucleated RBCs are RBCs that have left the bone marrow prematurely with a nucleus still intact and are considered immature RBCs. Under stress, the bone marrow releases nucleated RBCs to the peripheral circulation. Immature or nucleated RBCs should not be present outside of the early newborn period beyond the first week after birth. (8) The presence of nucleated RBCs outside of the neonatal period is highly suspicious for RBC pathology, such as acute leukemia, spleen dysfunction, anemia secondary to acute blood loss, or hemolysis.

One of the most important and often forgotten tests to help narrow the etiology of a RBC disorder is the reticulocyte count. The reticulocyte count helps differentiate between disorders of abnormal production, destruction, or loss of RBCs. Another very valuable laboratory test is the peripheral blood smear review, which should be considered as the next step in the evaluation of an abnormal CBC.

The basic definitions of RBC indices is included in this section to help clinicians understand the significance of abnormal results.

Hgb is the protein contained in RBCs that is responsible for delivery of oxygen to the tissues. The amount of Hgb in the blood is expressed in grams per deciliter (grams per liter).

Hematocrit (Hct) measures the proportion of RBCs compared with the total blood volume. Total blood volume includes WBCs, RBCs, platelets, and plasma. Hct is expressed as a percentage by volume and is approximately 3 times the value of Hgb. The clinical significance of Hgb and Hct are equivalent.

MCV measures RBC size and plays an important role in the diagnosis of RBC disorders. The MCV can be used to create different diagnostic categories to help quickly narrow the differential diagnosis of RBC disorders.

The RDW measures the range of RBC volume and size. An elevated RDW indicates different sizes of RBC populations (mixed normocytic cells and microcytic cells at the same time) caused by anisocytosis or variation in the size of the RBCs.

The RBC count is a direct measure of the amount of RBCs in whole blood. Elevation in the RBC count can be seen in patients with erythrocytosis, thalassemia, and Hgb variants with high oxygen affinity or can be falsely elevated in patients with severe dehydration.

The MCHC is a calculated index that measures the average amount of Hgb in the RBC. The MCHC can be helpful in classifying different types of anemia and can be affected by RBC hydration. MCHC is usually low in iron deficiency anemia and high (>35 g/dL [>35 g/L]) in hereditary spherocytosis.

RBC INTERPRETATION

The first step in RBC interpretation is to assess the Hgb value. Figure 1 provides a diagnostic algorithm for Hgb assessment, and Table 1 contains reference ranges for common RBC indices based on age and sex to aid in differentiation of normal versus high and low Hgb values. Anemia is defined as a reduction in RBC mass or blood Hgb concentration. (9) The limit for differentiating anemia from normal values is defined as 2 standard deviations (2 SD) below the mean for the normal population. The lower limit of a reference range depends on the population used to establish the reference range.

If the Hgb values are normal per the reference table, no further evaluation is necessary. Table 2 contains common RBC disorders paired with the expected laboratory results and next steps. If the Hgb is 2 SD above the mean, the CBC should be repeated to confirm that it is not a spurious result. If the value remains elevated, the clinician should evaluate for causes of erythrocytosis or polycythemia. The term

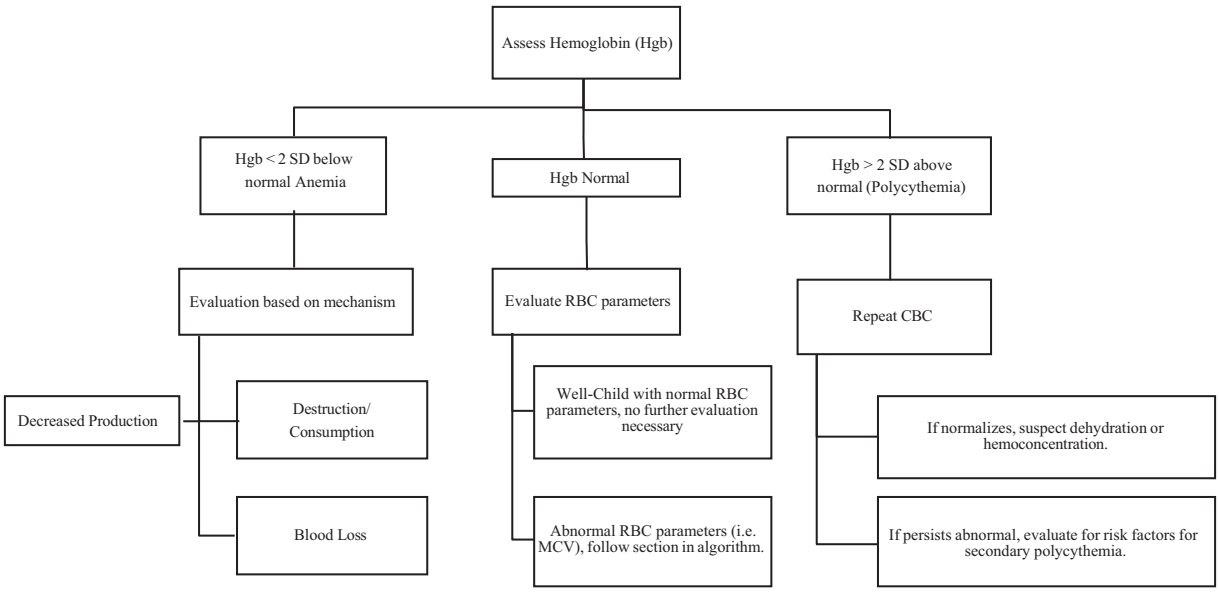

Figure 1. Initial evaluation of hemoglobin (Hgb) values. CBC=complete blood count, MCV=mean corpuscular volume, RBC=red blood cell.

erythrocytosis applies to an increase in circulating RBC mass to above the normal upper limits of 30 mL/kg body weight (excluding hemoconcentration due to dehydration). (10) In the United States, estimates of the RBC mass can be made using measured Hgb and Hct; in pediatrics, specific ranges exist for age and sex (Table 1). If the Hgb level is 2 SD below the mean, anemia is identified. The clinician should then consider the potential mechanism of anemia based on the patient's clinical history and physical examination findings, thinking of the broad categories of acute or chronic blood loss, and decreased RBC production, consumption, or destruction. To help determine the cause of anemia, the next best step is to obtain a reticulocyte count. If the reticulocyte count is elevated, the clinician should consider causes of destruction/consumption or blood loss, whereas if the reticulocyte count is low, the clinician should look for causes of decreased production. Abnormal production not due to nutritional deficiency should be referred to the pediatric hematologist-oncologist. In a patient with anemia, regardless of the reticulocyte count result, the next appropriate step is to review the peripheral blood smear for evidence of hemolysis or abnormal cell types.

A second strategy to help identify the etiology of anemia in a patient is to evaluate the RBC size as determined by the MCV. Figure 2 provides an algorithm for determining the cause of anemia based on MCV. Anemia with microcytosis or a low MCV (Fig 3) should prompt dietary evaluation for either nutritional causes (iron deficiency) or family history of microcytosis (thalassemia/rare hemoglobinopathies). Anemia with macrocytosis or a high MCV (Fig 4) should also prompt dietary evaluation for nutritional causes (folate or vitamin B_{12}) as well as for medication exposure. The third category, normocytic anemia (anemia with normal MCV), has the most diverse differential diagnosis. The reticulocyte count once again is very important to help differentiate the causes of normocytic anemia. If the clinician encounters a normocytic anemia with an elevated reticulocyte count, consideration of hemolysis or blood loss is important. If review of the peripheral blood smear shows evidence of hemolysis, the next most important blood test to perform is the direct antiglobulin test: a positive result indicates autoimmune hemolytic anemia, and a negative result could indicate a nonimmune acquired cause of hemolysis, such as microangiopathic hemolytic anemia or an inherited RBC defect such as spherocytosis (Table 2). A careful history and physical examination are necessary for evaluating a patient with normocytic anemia suspected to be due to blood loss. These patients will initially have a normal reticulocyte count but will develop reticulocytosis after 2 to 3 days of blood loss as the bone marrow responds appropriately to the anemia. A normocytic anemia with a low reticulocyte count indicates that the bone marrow is not able to respond normally to the presence of anemia. In this situation, the clinician should review other cell lines for additional cytopenias. Normocytic anemia with or without an elevated reticulocyte count most often requires referral to a pediatric hematology-oncologist. Patients who experience acute blood loss or hemolysis with an adequate bone marrow response should have a reticulocyte index higher than 3% for the response to be considered appropriate. Patients with inappropriate reticulocyte production usually have reticulocyte counts below 3%.

Table 1. RBC Indices in the Pediatric Population

Age	Hemoglobin, g/dL		Hematocrit, %		MCV, fL		RDW, %	RBC Count, $\times 10^6/\mu L$	MCH, pg	MCHC, g/dL	Reticulocytes, %
	Mean	2 SD	Mean	2 SD	Mean	2 SD	2 SD	Mean	Mean	Mean	Mean
Overall											
1–3 d	18.5	14.5–22.5	56.0	45.0–67.0	108	95–121	13.0–18.0	5.3	34	33	3.0
1 wk	17.5	13.5–19.5	54.0	42.0–66.0	107	88–126	13.0–18.0	5.1	34	33	0.5
2 wk	16.5	12.5–20.5	51.0	39.0–63.0	105	86–124	13.0–18.0	4.9	34	33	0.5
1 mo	14.0	10.0–18.0	43.0	31.0–55.0	104	85–123	11.5–16.0	4.2	34	33	0.8
2 mo	11.5	9.0–14.0	35.0	28.0–42.0	96	77–115	11.5–16.0	3.8	30	33	1.6
3–6 mo	11.5	9.5–13.5	35.0	29.0–41.0	91	74–108	11.5–16.0	3.8	30	33	0.7
0.5–2 y	12.0	10.5–13.5	36.0	33.0–49.0	78	70–86	11.5–16.0	4.5	27	33	1.0
2–6 y	12.5	11.5–15.5	37.0	34.0–45.0	81	75–87	11.5–15.0	4.6	27	34	1.0
6–12 y	13.5	11.5–15.5	40.0	35.0–45.0	86	77–95	11.5–15.0	4.6	29	34	1.0
Female sex											
12–18 y	14.0	12.0–16.0	41.0	33.0–51.0	90	78–102	11.5–14.0	4.6	30	34	1.0
≥18 y	14.0	12.0–16.0	41.0	33.0–51.0	90	80–100	11.5–13.1	4.6	30	34	1.0
Male sex											
12–18 y	14.5	13.0–16.0	43.0	36.0–51.0	88	78–198	11.5–14.0	4.9	30	34	1.0
≥18 y	15.5	13.5–17.5	47.0	37.0–53.0	90	80–100	11.5–13.1	5.2	30	34	1.0

Hgb=hemoglobin, Hct=hematocrit, MCH=mean corpuscular hemoglobin, MCHC=mean corpuscular hemoglobin concentration, MCV=mean corpuscular volume, RBC=red blood cell, RDW=red blood cell distribution width.

Patients with acute blood loss or rapid hemolysis with increased reticulocyte count can have elevated MCV related to the larger size of reticulocytes compared with mature RBCs. Similarly, transient erythroblastopenia of childhood initially presents as a normocytic anemia that becomes macrocytic as the marrow begins to recover. A normal marrow response with an increase in reticulocytes can lead to spurious macrocytosis reported by automatic laboratory instruments. In addition, disorders that cause RBC agglutination, and possibly reticulocytosis, such as autoimmune hemolytic anemias and mycoplasma infections, can elevate the MCV.

WHITE BLOOD CELLS

WBCs, the sentinels of the immune system, encompass multiple cell types, including granulocytes (neutrophils, eosinophils, and basophils), lymphocytes, and monocytes. WBC disorders may have increased, normal, or decreased cell numbers. Interpretation of WBC counts should be individualized based on the patient's age, clinical presentation, and risk factors. This section provides important tools to guide our understanding of the most common WBC disorders based on age. WBC numbers can show variations from normal values in many different clinical conditions. The presence of leukocytosis or leukopenia in a child with a recent infection would not warrant extensive evaluation for leukocytosis or leukopenia, whereas a child without known risk factors should receive further evaluation. In addition, review of the WBC differential count in a sick child may aid in narrowing the differential diagnosis for the type of infection (eg, lymphocytosis in pertussis). WBC life span in the peripheral blood varies by cell type.

As a general rule, every pediatric patient who has an abnormal WBC count on a CBC laboratory report should receive further evaluation. Many laboratory reports from community hospitals or rural communities usually follow adult reference ranges and may not be adjusted appropriately for pediatric patients. This laboratory practice can sometimes lead to misinterpretation and inappropriate diagnoses. Table 3 includes specific age-based WBC count ranges for newborns up to 21-year-old individuals to display variations by age. Recognizing age variations should always be the first step when evaluating a WBC count. If any WBC indices are out of range, the next step is to repeat a CBC with a differential count to rule out spurious results. If the repeated results are within the reference range and the patient has not developed any signs or symptoms suspicious for a pathologic disorder, no further evaluation is needed. If

Table 2. Red Blood Cell Disorders Laboratory Evaluation

Red Cell Disorders: Anemia (Hgb <2 SD for age)[a]	Peripheral Blood Smear	Other Findings/Associations
A. Decreased Production - associated with low Reticulocyte count		
Marrow Infiltration or Injury		
Malignancy	Blasts (suggestive of leukemia) nRBCs	Other cytopenia (thromcytopenia and leukopenia) or leukocytosis
Infiltration		Metabolic disorders
Infections	Usually normal findings	Transient, recovers in approximately 2-3 weeks
Nutritional Deficiency		
Iron Deficiency Anemia	Microcytic, Hypochromic red cells	↓MCV, ↓ Reticulocyte, ↑RDW, ↑ TIBC, ↓ferritin, ↓serum iron, ↓tf saturation
Vitamin B12 deficiency	Megaloblasts, Reticulocytopenia, Hypersemented Neut	↑MCV >110 ft; Pancytopenia, ↑MMA, ↑homocysteine, Neurological abnormalities
Folate deficieny	Megaloblasts, Reticulocytopenia, Hypersemented Neut	↑ MCV >110ft, Pancytopenia, NI MMA, ↑homocysteine
Lead toxicity	Basophilic stippling	↓MCV
Erythropoietin Deficiency		
CKD	Normocytic anemia	NI MCV, history of chronic renal disease
Congenital EPO deficiency (rare)		Absent or very low EPO level
Ineffective Erythropoieis		
TEC	Anemia with reticulocytopenia-healthy child	Spontaneous/transient and self-limited interrupted erythropoieses
Aplastic anemia	Pancytopenia after inciting event	Plt<20,000/mL, ANC <500/mL & Retic <1% corrected- ↑MCV with normal RDW
Infection related (Parvo B19)		↓Reticulocyte count
Splenectomy	Howell-Jolly bodies	Acquired vs congenital
Sideroblastic anemia	Pappenheimer bodies	Diagnosis of exclusion
BMF-Fanconi Anemia	Macrocytosis	Congenital anomalies-not always present [radial deformities, café au lait, short stature]
BMF-Diamond Blackfan Anemia	Macrocytosis	↑MCV in a young child <1 yo; reticulocytopenia; congenital anomalies-short stature and bony
Anemia of chronic disease/Inflammation		Other chronic medical conditions, normal to microcytic MCV
Hypothyroidism		
B. Hemolysis - associated with elevated reticulocyte count		
Acquired Causes - Extrinsic to RBC		Usually associated with ↑IB, ↑LDH, ↓↓haptoglobin
Immune Causes (+DAT)		
Warm AIHA	Schistocytes	Secondary casues- immune deficiencies, rheumatologic, Evan's sybdrome, Hodgkin, others
Cold Agglutinin (*Mycoplasma,* EBV)		Self-limited
Paroxysmal cold hemoglobinuria (Viral)		Self-limited
HDN (ABO, Rh, other minor groups)	Schistocytes in the newborn	↑IB, ↑LDH; Self-limited
Non-immune casues (-DAT)		
Recent infections		Resolves within 2-3 weeks
Medications		Resolves with medication discontinuation; haptenized red cell proteins
Mechanical (CHD/Hemangiomas)	Schistocytes	
Burns	Bizarre shape, poikilocytosis, fragmentation, microsphere	
HUS	Schistocytes	Typical (renal dysf, mild-mod thrombocytopenia), bloody diarrhea
aHUS	Schistocytes	Renal dysf, mild-mod thrombocytopenia, +/- infectious symp

Continued

Table 2. Red Blood Cell Disorders Laboratory Evaluation (Continued)

Red Cell Disorders: Anemia (Hgb <2 SD for age)[a]	Peripheral Blood Smear	Other Findings/Associations
TTP	Schistocytes	Fever, ↓plt, renal dysfunction, neurologic changes; N/I PT/PTT/Fibrinogen
PNH	Schistocytes	Acquired clone (absent CD55/CD59); hemoglobinuria, risk for thrombosis
Inherited Causes - Intrinsic to RBC	Appropriately compensated reticulocytosis with hemolytic events	
Membrane disorders-Hab range varies		
Hereditary Spherocytosis (HS)	Sphereical red cell shape in >25%; microspheres	Anemia (varies with mutations), AD>AR inheritance, ↑MCHC, ↑IB, ↑LDH
Hereditary Elliptocytosis	Ellipitical red cell shapes in >25%;`cigar shape'	Varies from mild to severe hemolytic anemia
Hereditary Pyropoikilocytosis (HPP)	Bizarre shape, poikilocytosis, fragmentation, microsphere	↓MCV, very rare, subtype of HE
Hereditary Stomatocytosis	Stomatocytes "mouth shape RBC"	↑MCV, ↓MCHC,`dehydrated'
Hereditary Xerocytosis	Stomatocytes "mouth shape RBC"	↑MCV, ↑MCHC, 'overhydrated'
Enzyme disorders		
G6PD	Heinz bodies, blister cells	Classes I-IV (based on enzyme activity level); Episodic anemia with triggers
PKD, Hexokinase deficiency, others		
Hemoglobinopathies		
Sickle Cell Disease	Sickled RBC	Hemoglobin electrophoresis/analysis or Newborn Screen for diagnosis; varying degrees of anemia
Thalassemias	Basophilic stippling, target cells	Hemoglobin electrophoresis/analysis or Newborn Screen for diagnosis; varying degrees of anemia
C. Blood Loss - associated with elevated reticulocyte count		
Bleeding Disorders (vWD, Hemophilia, etc)		
GI blood loss		
AUB (hormonal, vWD, etc)		
Trauma		

AD=autosomal dominant, aHUS=atypical hemolytic uremic syndrome, AIHA=autoimmune hemolytic anemia, ANC=absolute neutrophil count, AR=autosomal recessive, AUB=abnormal uterine bleeding, BMF=bone marrow failure, CHD=congenital heart disease, CKD=chronic kidney disease, DAT=direct antiglobulin test, EBV=Epstein-Barr virus, EPO=erythropoietin, G6PD=glucose-6-phosphate dehydrogenase deficiency, Hbg=hemoglobin, HDN=hemolytic disease of the newborn, HUS=hemolytic uremic syndrome, IB=Indirect Hyperbilirubinemia, LDH=lactate dehydrogenase, MCHC=mean corpuscular hemoglobin concentration, MCV=mean corpuscular volume, MMA=methylmalonic acidemia, NI=normal, PKD=pyruvate kinase deficiency, PNH=paroxysmal nocturnal hemoglobinuria, PT/PTT=prothrombin time/partial thromboplastin time, RBC=red blood cell, RDW=red blood cell distribution width, TIBC=total iron binding capacity, TTP=thrombotic thrombocytopenic purpura, vWD=von Willebrand disease.
[a]Isolated abnormal red cell parameters should warrant a repeat CBC to rule out spurious causes if no clinical correlation.

after repeating the CBC, the abnormal findings persist, the investigation process should begin. Depending on the clinical setting, it is reasonable to repeat the CBC with a differential cell count within 2 to 4 weeks of the initial abnormal result. Most of the common acquired neutropenias or lymphopenias are transient and tend to resolve within a few weeks. (11) Patients who have persistent abnormalities of cell quantity should obtain an evaluation from a pediatric hematologist-oncologist.

WBCs are broadly divided into 2 major groups: granulocytes and agranulocytes. Granulocytes include neutrophils, basophils, and eosinophils. Cells without granules in the cytoplasm, agranulocytes, include monocytes and lymphocytes. Each WBC has a specific role in the immune system, and variations in quantity of the specific cell type are associated with different pathologic processes. It is important to understand that calculating the absolute count of a specific cell type gives more information about the risk of pathologic conditions. Absolute counts also vary with age, and age-specific ranges exist (Table 3).

Leukocytosis is defined as an increase in the total WBC count more than 2 SD above the mean for age. Leukopenia is usually defined as a total WBC count less than 4,000/μL (4×10^9/L). For clarity, we recommend first evaluating the total WBC count and then evaluating the absolute cell counts for neutrophils, monocytes, lymphocytes, and eosinophils. Subsequent evaluation can then be tailored by cell type. The WBC count reported by automated instruments may be affected by the presence of other cells that are incorrectly classified. For example, nucleated RBCs that are

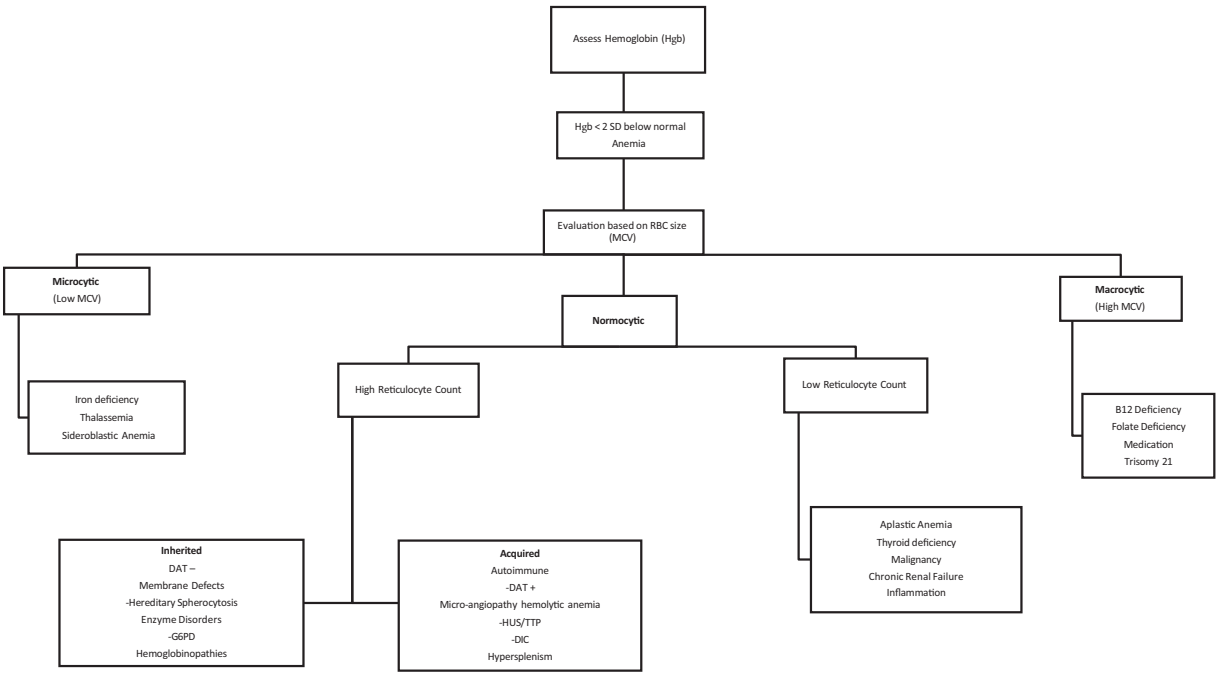

Figure 2. Evaluation of anemia based on red blood cell (RBC) size (mean corpuscular volume [MCV]). DAT=direct antiglobulin test, DIC=disseminated intravascular coagulopathy, G6PD=glucose-6-phosphate dehydrogenase, Hgb=hemoglobin, HUS=hemolytic uremic syndrome, TTP=thrombotic thrombocytopenic purpura.

produced as part of the normal bone marrow response in conditions such as hemolytic anemia or marrow infiltration can cause a falsely elevated WBC count. In such conditions, the laboratory should report an adjusted WBC count, which should be used in the calculations of absolute cell counts. To calculate the absolute cell count, multiply the percentage of cell type by the total leukocytes per cubic millimeter (absolute cell count = WBC count × 1,000 × % cell type). For example, to calculate the absolute neutrophil count (ANC), multiply the total WBC count by the percentage of neutrophils and bands. The same calculation can be performed for lymphocytes and eosinophils.

WBC INTERPRETATION

After assessment of the Hgb and RBC indices, the CBC should be evaluated for WBC abnormalities. The total WBC count should first be reviewed. Table 3 provides age-specific

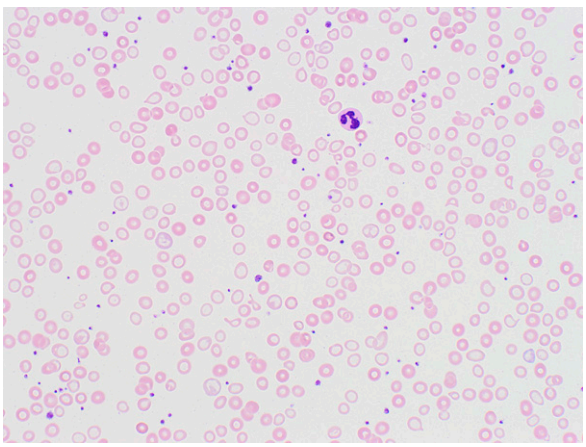

Figure 3. Wright-stained peripheral blood smear (×40) from a patient with iron deficiency anemia shows microcytic, hypochromic anemia and associated reactive thrombocytosis.

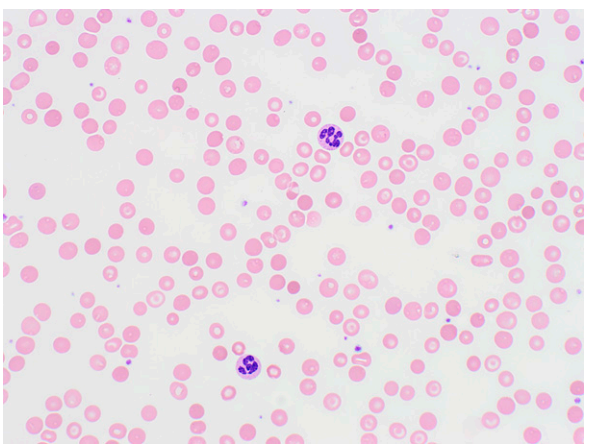

Figure 4. Wright-stained peripheral blood smear (×40) from a patient with folate deficiency shows macrocytic anemia and characteristic hypersegmentation of neutrophils.

Table 3. WBC Parameters in the Pediatric Population

Age	WBC Count, $10^3/\mu L$		Neutrophil Count, $10^3/\mu L$			Lymphocyte Count, $10^3/\mu L$			Eosinophil Count, $10^3/\mu L$		Monocyte Count, $10^3/\mu L$	
	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	0.4	2	1.1	6
12 h	22.8	13.0–38.0	15.5	6.0–28.0	68	5.5	2.0–11.0	24	0.5	2	1.2	5
24 h	18.9	9.4–34.0	11.5	5.0–21.0	61	5.8	2.0–11.5	31	0.5	2	1.1	6
1 wk	12.2	5.0–21.0	5.5	1.5–10.0	45	5.0	2.0–17.0	41	0.5	4	1.1	9
2 wk	11.4	5.0–20.0	4.5	1.0–9.5	40	5.5	2.0–17.0	48	0.4	3	1.0	9
1 mo	10.8	5.0–19.5	3.8	1.0–9.0	35	6.0	2.5–16.5	59	0.3	3	0.7	7
6 mo	11.9	6.0–17.5	3.8	1.0–8.5	32	7.3	4.0–13.5	61	0.3	3	0.6	5
1 y	11.4	6.0–17.5	3.5	1.5–8.5	31	7.0	4.0–10.5	61	0.3	3	0.6	5
2 y	10.6	6.0–17.0	3.5	1.5–8.5	33	6.3	3.0–9.5	29	0.3	3	0.5	5
4 y	9.1	5.5–15.5	3.8	1.5–8.5	42	4.5	2.0–8.0	50	0.3	3	0.5	5
6 y	8.5	5.0–14.5	4.3	1.5–8.0	51	3.5	1.5–7.0	42	0.2	3	0.4	5
8 y	8.3	4.5–13.5	4.4	1.5–8.0	53	3.3	1.5–6.8	39	0.2	3	0.4	4
10 y	8.1	4.5–13.5	4.4	1.8–8.0	54	3.1	1.5–6.5	38	0.2	2	0.4	4
16 y	7.8	4.5–13.0	4.4	1.8–8.0	57	2.8	1.2–5.2	35	0.2	3	0.4	5
21 y	7.4	4.5–11.0	4.4	1.8–7.7	59	2.5	1.0–4.8	34	0.2	3	0.3	4

WBC = white blood cell.
[a]Documented normal absolute neutrophil count for age in the past.

reference ranges for total WBC count and individual cell types, and Fig 5 provides an algorithm for general WBC count assessment. If the total WBC count is normal (within 2 SD of the mean for age in a healthy infant or child), the differential cell count should be evaluated next and absolute counts calculated to identify cell abnormalities associated with disease, such as neutropenia, lymphopenia, or eosinophilia. If a specific cell abnormality is identified, Figs 6, 7, and 8 provide evaluation steps for neutropenia, lymphopenia, and eosinophilia, respectively. If absolute counts are normal, no further evaluation is necessary.

If the total WBC count is identified as less than 4,000/μL (4×10^9/L) or 2 SD below the mean, the history and physical examination become important for determining the next steps for a healthy or sick child. Each cell type should be evaluated for evidence of cytopenia to determine whether the low total WBC count is due to overall deficiency or to reduced numbers of a specific cell type (see Table 3 for reference ranges). If severe leukopenia or other low absolute cell count is identified in an asymptomatic child, a repeated CBC with a differential cell count should be performed with a review of the peripheral blood smear. If there are no abnormal findings on review of the peripheral blood smear, a CBC with differential cell count should be repeated within 2 to 4 weeks. If the repeated CBC shows the leukopenia or other low absolute cell count to have resolved, the low cell count is likely to be transient, and no further investigation is warranted. If the patient has a recent history of a viral or bacterial infection, abnormal cell counts should resolve within 2 to 4 weeks. However, in young children who may have multiple viral infections, WBC count recovery may be prolonged and could take up to 12 weeks.

If the total WBC count is more than 2 SD above the mean for age, the patient's history and physical examination findings should be reviewed for signs of infection. Next, the differential cell count for each specific cell type should be determined. In a patient with acute infection, neutrophilia or lymphocytosis may cause the elevated WBC count, which may be related to the underlying infection. The presence of immature or abnormal WBCs on the differential count should prompt a peripheral blood smear review and consultation with pediatric hematology-oncology. It is important to assess the overall CBC for the presence of concomitant cytopenias (anemia or thrombocytopenia), which, if present, warrants referral to pediatric hematology-oncology. For asymptomatic patients or those with confirmed infection, a repeated CBC in 2 to 4

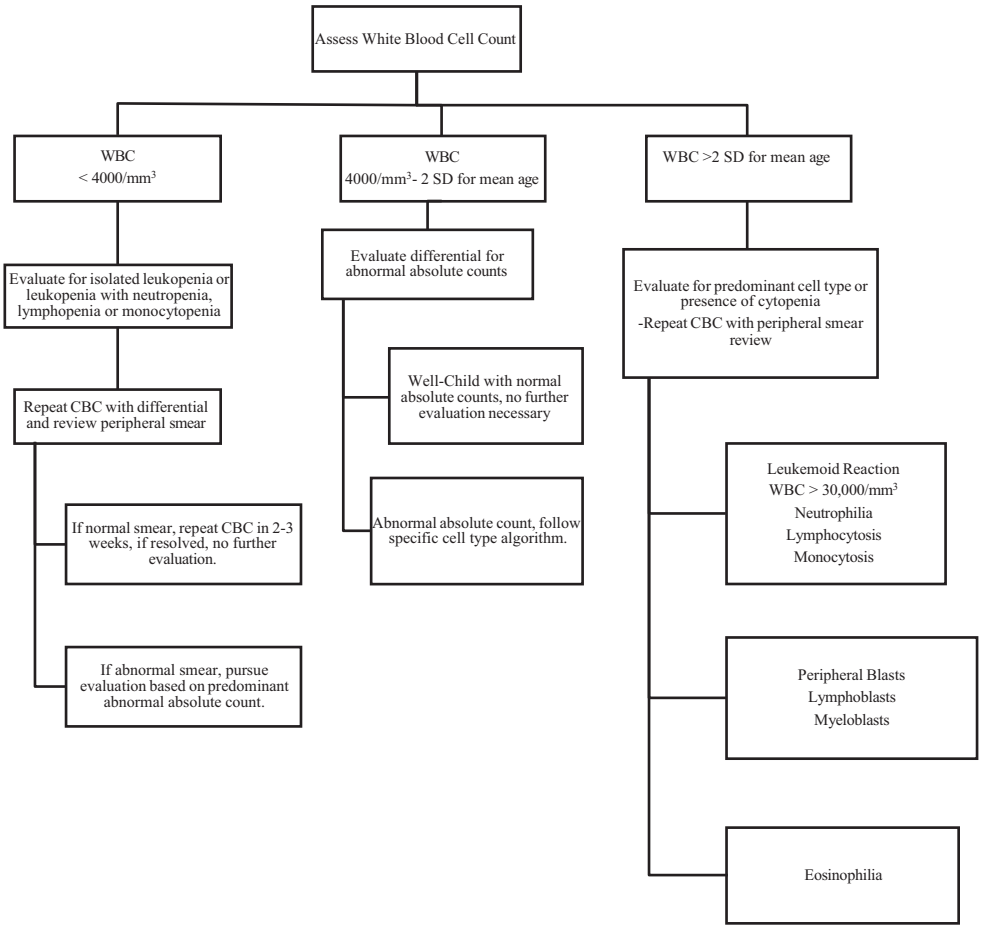

Figure 5. Initial evaluation of white blood cell (WBC) count. CBC=complete blood count.

weeks should show results returning to normal, making additional evaluation unnecessary. However, if WBC cytopenia persists, evaluation should continue as recommended in the next sections.

NEUTROPHILS

The identification of neutropenia in pediatric patients can evoke anxiety in both clinicians and caregivers. The mechanism, severity, and duration of neutropenia are associated with different risks of infection. Neutropenia severity for children older than 18 months to 2 years of age is defined as mild, when the ANC is 1,000 to 1,500/μL ($1–1.5\times10^9$/L); moderate, for an ANC of 500 to 1,000/μL ($0.5–1\times10^9$/L); and severe, for an ANC less than 500/μL ($<0.5\times10^9$/L). It is important to understand that the normal number of neutrophils also changes with age and that neonatal values are different due to the surge of neutrophil production from the bone marrow secondary to the stress of delivery, with subsequent decrease in the bone marrow proliferative pool after birth. (12) For infants and children, neutropenia is defined as ANC less than 1,000/μL ($<1\times10^9$/L) until 2 years of age.

Etiologies of neutropenia include increased neutrophil destruction or consumption, often acquired, and decreased production as seen in inherited causes. The history and physical examination are extremely important for determining the cause of neutropenia. Children with neutropenia and a history of chronic infections with mucocutaneous findings raise suspicion for inherited causes and often have prolonged periods of neutropenia, and children with the more commonly acquired causes tend to have self-limited neutropenia. Figure 6 provides an algorithm for evaluating neutropenia, and Table 4 provides information on common disorders of neutrophils.

In a patient with acute infection and neutropenia, the CBC with differential cell count should be repeated within 2 to 4 weeks after resolution of symptoms. If neutropenia resolves, no further evaluation is necessary, and the neutropenia was likely due to an infection or medication suppression. If neutropenia persists for more than 8 weeks or

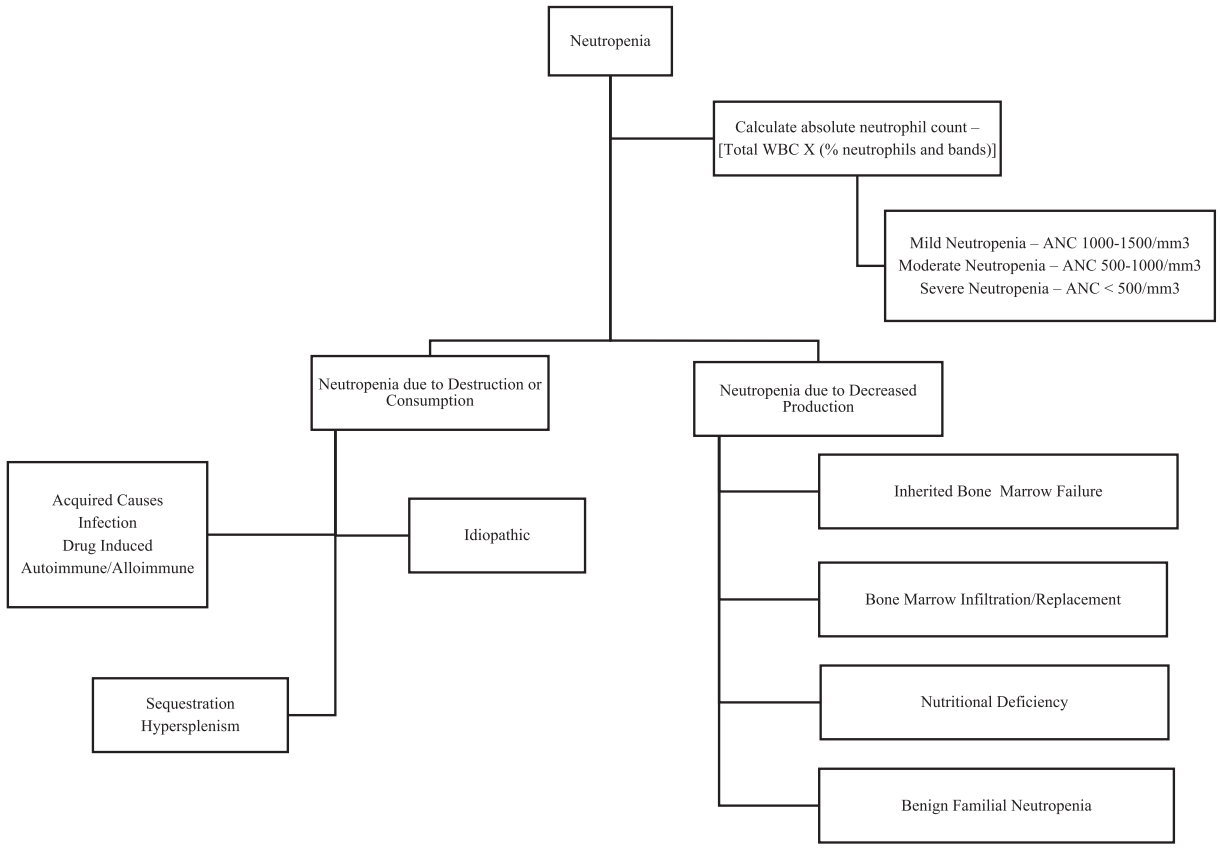

Figure 6. Diagnostic approach for neutropenia. ANC=absolute neutrophil count, WBC=white blood cell.

any additional cytopenia is found, a referral to pediatric hematology-oncology is warranted. If neutropenia is identified in patients taking long-term medications such as antipsychotic, antiseizure, or other immunosuppressive medications, and if treatment change is not possible, a CBC should be repeated in 2 to 4 weeks; if neutropenia persists, an alternative treatment should be considered, with referral to pediatric hematology-oncology.

Neutropenia identified in newborns and infants often requires more follow-up than neutropenia in older children. Neonatal neutropenia is common in the setting of infection, but newborns may also have neutropenia due to maternal antibodies (alloimmune neutropenia). Moreover, various congenital neutropenia disorders present early in childhood, with affected children developing serious and recurrent infections.

A child with a history of recurrent infections, poor growth, and/or phenotypic abnormalities, and persistent neutropenia with an ANC less than 1,500/μL ($<1.5\times10^9$/L), warrants referral to pediatric hematology-oncology to evaluate for inherited bone marrow failure. In a child with a history of bone pain, prolonged fever, or unexplained fatigue with evidence of neutropenia or leukopenia and additional cytopenias (anemia or thrombocytopenia), a physical examination should be performed for lymphadenopathy and hepatosplenomegaly. A blood specimen should be sent for peripheral blood smear review, lactate dehydrogenase level, uric acid level, complete metabolic panel, and referral to pediatric hematology-oncology to evaluate for possible leukemia. Pediatric leukemia may present with a high or low WBC count but does not always present with pancytopenia. Instead, there may be leukopenia and neutropenia accompanied by either mild anemia or thrombocytopenia.

If isolated neutropenia (normal total WBC count) is identified on a routine screening CBC and the child has no recent illness, a CBC with differential cell count should be repeated in 2 to 4 weeks. If neutropenia persists, one should consider consultation with pediatric hematology-oncology for evaluation for benign neutropenia of childhood. Persistent neutropenia in a healthy child with no obvious phenotypic abnormalities or recurrent infections is considered benign and may be attributed to benign familial neutropenia. Historically, a condition termed *benign ethnic neutropenia* has been described among individuals of African ancestry in which the ANC is chronically between 1,000/μL (1×10^9/L) and 1,500/μL (1.5×10^9/L). This is no longer considered a medical condition

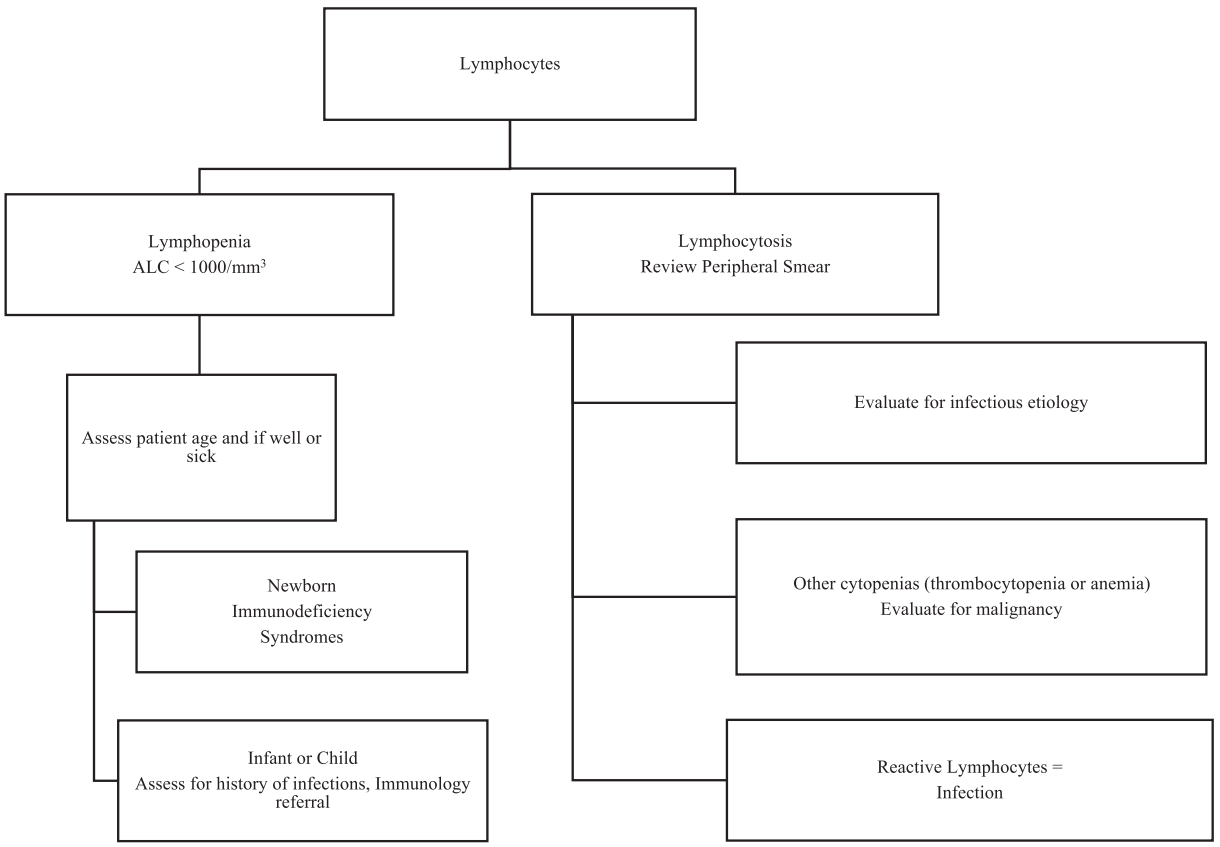

Figure 7. Diagnostic approach for lymphocytosis and lymphopenia. ALC=absolute lymphocyte count.

but represents white-centric reference ranges. (13) In an otherwise healthy child who is younger than 2 years with an ANC less than 1,500/μL (<1.5×10^9/L), one should repeat a CBC after the child is 2 years old, and if the CBC is normal, no further management is needed. Premature infants and infants younger than 6 months with an ANC of 1,000/μL (1×10^9/L)

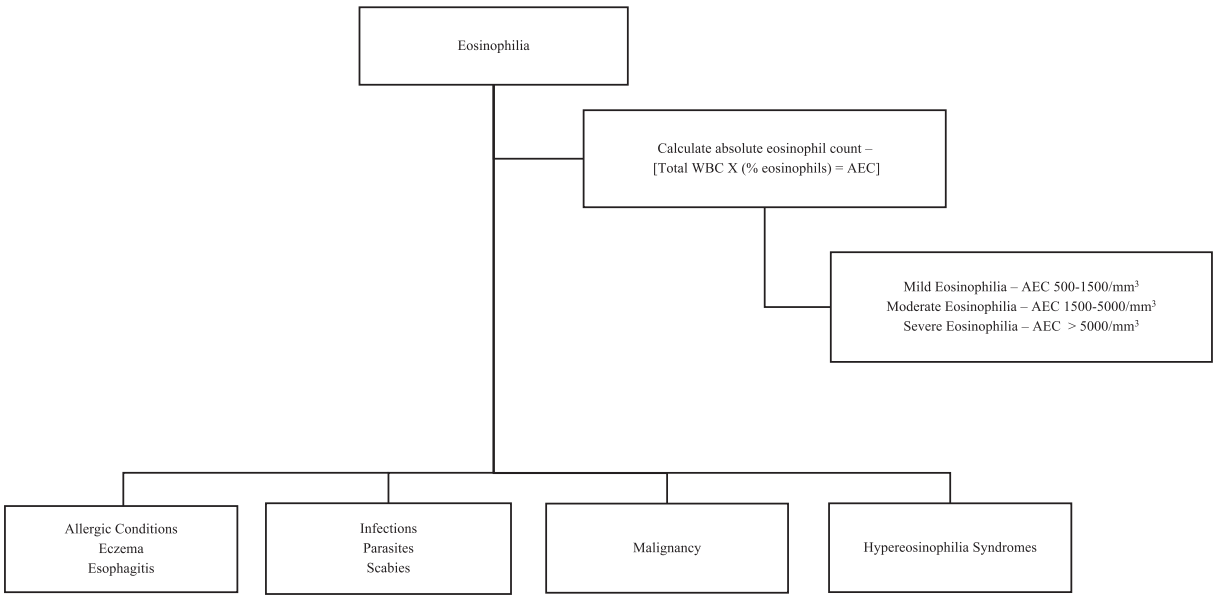

Figure 8. Diagnostic approach for eosinophilia. AEC=absolute eosinophil count, WBC=white blood cell.

Table 4. White Blood Cell Disorders and Laboratory Evaluation

Disorders	Cause	Other Findings/Associations
Neutrophils		
Neutropenia (acquired causes)[a]		
Infection-transient suppression	Most common is viral etiology	Most common cause of acquired neutropenia; self-limiting by 3 mo
Autoimmune neutropenia (chronic benign neutropenia)	Antineutrophil antibody	Age of presentation: 3–30 mo; less likely to have serious infections; spontaneous resolution
Chronic idiopathic	Unknown etiology	Diagnosis of exclusion; no attributable underlying cause; spontaneous resolution
Drug-induced	BM suppression or immune mediated	Chemotherapy, sulfonamides, antibiotics, AEDs, NSAIDs, antihistamines- improves with drug cessation
DIC/sepsis	Consumption	Transitory; resolves with treatment of underlying [infection, malignancy, etc]
Splenic sequestration	Consumption/destruction	Associated with portal hypertension, cyanotic heart disease, infiltration
Malignancy	Immature cells/pancytopenia	Bone Marrow infiltration (leukemia, lymphoma, solid tumors: neuroblastoma, rhabdomyosarcoma, Ewing)
Aplastic anemia	Stem cell failure	Pancytopenia with low reticulocyte count and immature platelet fraction
Nutritional deficiencies	Vitamin B_{12}/folate/copper deficiency	Megaloblasts, reticulocytopenia, hypersegmented neutrophils
Neonatal neutropenia	Multiple causes	Pre-term infant, maternal hypertension or preeclampsia; Sepsis
Neonatal alloimmune	Fetal-maternal incompatibility	Immediate newborn period; spontaneous resolution in first 3-6 mo after birth; transplacental ab's [HNA-1b/-2a]
Neonatal isoimmune	Transplacental IgG antibodies	Mother with autoimmune neutropenia; spontaneous resolution in 3–6 mo
Increased destruction	BM toxicity/peripheral destruction	Chemotherapy; radiation to long bones; ECMO; mechanical valves
PNH	Acquired stem cell defect	Pancytopenia, thrombosis
Neutropenia [congenital causes]		
Fanconi anemia	BMF; *FANC* mutations, multiple	Congenital anomalies-not always present [radial deformities, café au lait, short stature]; ↑MCV
Dyskeratosis congenita	BMF; telomerase defects	Dysplastic nails; oral leukoplakia; lacy reticular pigmentation usually by age 10 y; H&N solid tumors; PF
Shwachman-Diamond	BMF; *SBDS* mutation	Exocrine pancreatic insufficiency, short stature, skeletal anomalies; FTT at 1 y of age; M>>F; ↑HgbF
Severe congenital (SCN)	BMF; *ELA2, CSFR3, WASP* mutations	Invasive bacterial infections; ANC <200; omphalitis, cutaneous
Chediak-Higashi syndrome	Mutations in *LYST*, impaired chemotaxis	Oculocutaneous albinism and recurrent infections (skin, lungs and mucocutaneous); qualitative disorder
Griscelli syndrome type II	*RAB27α* mutation	Partial albinism (silver hair), HLH
Hermansky-Pudlak type 2	*AP3p1* mutation	Nystagmus, oculocutaneous albinism, skin hypopigmentation; PF; colitis; cyclic neutropenia
WHIM syndrome	Gain of function mutation in *CXCR4*	Warts (HPV), hypogammaglobulinemia, severe neutropenia, infections-impaired release of neutrophils
Cyclic neutropenia	*ELA2* mutation	Mouth ulcers with fever, recurrent infections, adenopathy- every 21 days and lasts 2-6 days
Benign ethnic	Absence of other causes	Absent recurrent infections; certain ethnic groups; diagnosis of exclusion
Benign familial	Absence of other causes	Absent recurrent infections; family history of neutropenia; diagnosis of exclusion
Immunodeficiencies	Varies	Recurrent infections and FTT at a very young age
Metabolic disorders	Varies	Orotic aciduria, methylmalonic aciduria, hyperglycinemia & Glycogen storage disease type 1b

Continued

Table 4. White Blood Cell Disorders and Laboratory Evaluation (Continued)

Disorders	Cause	Other Findings/Associations
Lymphocytes: Age-dependent values; see Table # for adequate ranges.		
Lymphocytosis-primary	Absence of secondary causes and consistent elevation of lymphocytes-evaluated for congenital cause	
BENTA	*CARD11* mutation	B-cell lymphocytosis and immunodeficiency; splenomegaly, lymphadenopathy and recurrent sinopulm infxns
Lymphocytosis-secondary		
Infection	Viral, bacterial, and parasites (multiple)	EBV and CMV are the most common- atypical lymphocytosis; acute HIV; Toxoplasma gondii, B. pertussis
Medication-induced	Allopurinol, AEDs, sulfa, sulfonamides	DRESS-also associated with eosinophilia
Malignancy	ALL/lymphoma, CLL, NHL	Usually monomorphic lymphocytosis
Splenectomy		
Lymphocytopenia-primary		
SCID	Absent TRECs on newborn screen	Warrants further evaluation; total CD3+ count <300 cells/μL
X-linked agammaglobulinemia	B-cell deficiency	Low imunoglobulin levels
Lymphocytopenia-secondary		
Medication-induced	Multiple	Glucocorticoids, chemotherapy, monoclonal anotibodies, rituximab
Infections	Multiple	Chronic HIV; viral infections, bacterial-ehrlichiosis, S. typhi, leptospirosis, tuberculosis, sepsis
Malignancy	Lymphoma, solid tumors	
Autoimmune disorders	Crohn disease, MIS-C, SLE, DM1, vasculitis, RA	Reactive/inflammation
Other causes	ESRD, burns, zinc deficiency, lymphatic malfunction	
Eosinophils		
Eosinophilia	Most common are secondary causes	
For children: (500–1,000-mild); (1,500–5,000-moderate); (>5,000-severe)		
Infection	Bacterial, parasites, fungal, viral, helminth	Resolves with treating underlying etiology
Medication-induced	Antibiotics, antidepressants, NSAIDs	Usually cause severe eosoniphilia with counts >20,000/μL
Immune disorders	ALPS, SCN, WAS, Job syndrome, Ommen	
Autoimmune/inflammatory	IBD, IBS, SLE, arthritis; sarcoidosis	
Allergy	Allergic rhinitis, asthma, atopic dermatitis	Most common cause in the United States
Malignancy	ALL, HL, and others	
Other causes	SCD, radiation induced; hypoadrenalism	
Primary eosinophil deficiency	Extremely rare	Familial eosinophilia syndrome; hyperosinophilic syndrome
Secondary eosinophil deficiency	Associated with secondary causes	Medications, infections, other medical conditions

AED=antiepileptic drugs, ALL=acute lymphoblastic leukemia, ALPS=autoimmune lymphoroliferative syndrome, BENTA=B-cell expansion with NF-κB and T-cell anergy, CLL=chronic lymphocytic leukemia, BM=bone marrow, BMF=bone marrow failure, CMV=cytomegalovirus, DIC=disseminated intravascular coagulopathy, DM1=diabetes mellitus type I, DRESS= drug reaction with eosinophilia and systemic symptoms, EBV=Epstein-Barr virus, ECMO=extracorporeal membrane oxygenation, ESRD=end-stage renal disease, FTT=failure to thrive, H&N=head and neck, HIV=human immunodeficiency virus, HL=Hodgkin lymphoma, HLH=hemophagocytic lymphohistiocytosis, HPV=human papillomavirus, IBD=inflammatory bowel disease, IBS=irritable bowel syndrome, MCV=mean corpuscular volume, MIS-C=multisystem inflammatory syndrome in children, NHL=non-Hodgkin lymphoma, NSAID=nonsteroidal anti-inflammatory drugs, RA=rheumatoid arthritis, PF=pulmonary fibrosis, PNH=paroxysmal nocturnal hemoglobinuria, SCID=severe combined immunodeficiency, SCN=severe congenital neutropenia, SLE=systemic lupus erythematosus, TREC=T-cell receptor excision circles, WAS=Wiskott-Aldrich syndrome.
[a]Neutropenia is defined as an ANC/μL: For term newborns–1 week of age, ANC<3,000/μL; for 1 week to 2 years of age, <1,000/μL; for 2 years and older, normal—1,000–1,500/μL, mild—500–1,000 /μL, moderate—250–500/μL, severe—<250/μL.

or less are considered to be normal in the absence of recurrent infections because children's neutrophil counts do not reach adult neutrophil values of 1,500/μL (1.5×10^9/L) until after 2 years of age.

LYMPHOCYTES

Lymphocytes include T lymphocytes, B lymphocytes, and natural killer cells. These cells play an important role in the immune system. Figure 7 provides an algorithm for evaluating lymphocytosis or lymphopenia. Tables 3 serves as a reference for age-related lymphocyte values. Children will have predominant numbers of lymphocytes during the first 2 years after birth.

During evaluation of the total WBC count, an elevated number of lymphocytes or lymphocytosis may be identified. Lymphocytosis usually represents a reactive, self-limited

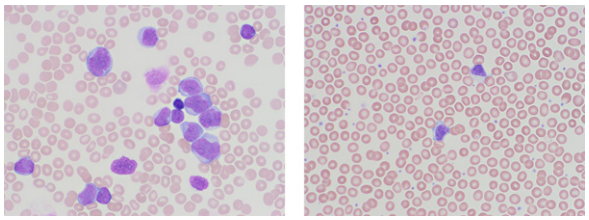

Figure 9. Comparison of blasts (left) and reactive lymphocytes (right) (magnification ×60). The lymphoblasts on the left are large (see normal lymphocytes among the blasts for size comparison), with irregular nuclear contours, open chromatin, and conspicuous nucleoli. The reactive lymphocytes on the right demonstrate angulated nuclei with condensed, mature chromatin.

process in the setting of infection, with the lymphocyte count returning to normal after the underlying cause resolves. However, the primary clinical concern with lymphocytosis is that it may represent a malignant process, such as acute leukemia. In a child with a recent infection, lymphocytosis is caused by reactive lymphocytes, which can be seen on review of the peripheral blood smear. Lymphocytosis in this setting is not due to clonal expansion of an abnormal cell population, but to a normal lymphocyte response to an infection. Patients with a lymphoid malignancy will often have additional cytopenias, suspicious symptoms, and abnormal physical examination findings. In lymphoid malignancy, the abnormal lymphoid cells seen in the peripheral blood smear would be lymphoblasts and not reactive lymphocytes.

Lymphocytes that have become normally activated in response to infection were previously called *atypical* lymphocytes, which concerned clinicians that these cells may represent leukemia cells. As a result, laboratory nomenclature now refers to these cells as *reactive* lymphocytes (Fig 9) to better indicate an infectious etiology and minimize concern for malignancy. If a patient with lymphocytosis is reported as having atypical lymphocytes rather than reactive lymphocytes, the peripheral blood smear should be reviewed with an experienced pathologist, as some laboratories may still use old terminology, and if inexperienced in identifying lymphoblasts, a laboratory may incorrectly call lymphoblasts

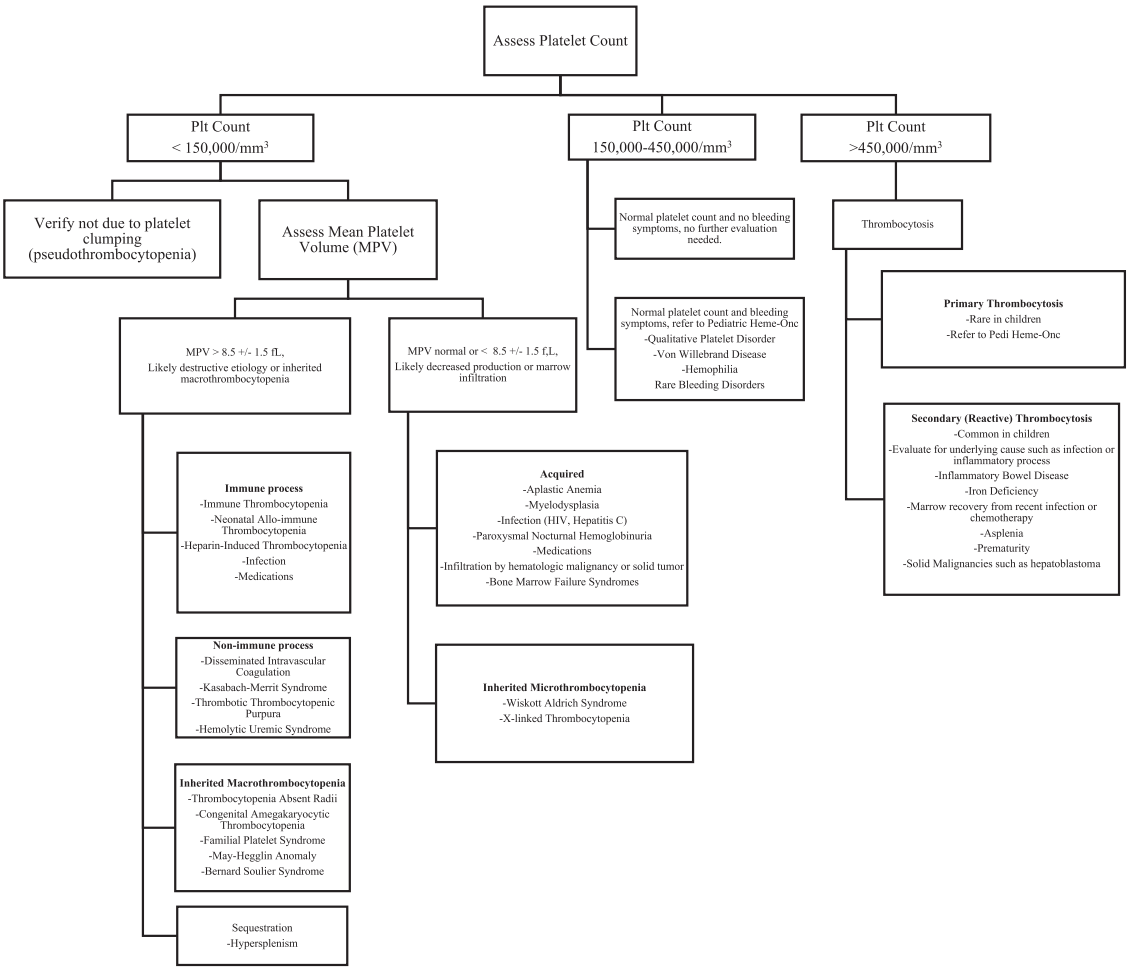

Figure 10. Diagnostic approach for thrombocytopenia and thrombocytosis. HIV=human immunodeficiency virus, MPV=mean platelet volume.

"atypical lymphocytes." Any suspicion for malignancy, such as additional cytopenia or the child appearing "toxic," should prompt a peripheral blood smear review with pathology and possible flow cytometry.

If during evaluation of the total WBC count lymphopenia is found, defined as absolute lymphocyte count less than 1,000/μL ($<1\times10^9$/L), Fig 7 can be used to guide patient evaluation, and Table 4 includes common diagnoses with associated laboratory results.

EOSINOPHILS

Eosinophils are 1 of the granulocytic cells of myeloid origin. The most common causes of eosinophilia in the United States include allergies and medications. During review of the total WBC count, it is important to review the automated absolute eosinophil count (AEC) or calculate it if it is not included on the differential report. Eosinophilia is defined as mild when the AEC is 500 to 1,500/μL ($0.5–1.5\times10^9$/L); moderate when the AEC is 1,500 to 5,000/μL ($1.5–5\times10^9$/L); and severe, for an AEC greater than 5,000/μL ($>5\times10^9$/L). Figure 8 provides an algorithm for the evaluation of eosinophilia.

MONOCYTES AND BASOPHILS

Monocytes, 1 of the largest leukocytes, differentiates into macrophages and dendritic cells that phagocytose and digest microbes. Basophils play a role in inflammation. The absolute number of these cell types will be low in total leukopenia or reduced in a proliferative disorder such as leukemia. Isolated abnormalities in the quantity of these cells warrant special attention because disorders involving monocytes or basophils are extremely rare. If review of the total WBC count demonstrates specifically low or high monocyte or basophil counts, the next step is to always repeat the CBC with a differential cell count within the next 2 to 4 weeks. For patients with persistence of abnormal basophil or monocyte counts, one should consult pediatric hematology-oncology.

For any patient who has an absolute monocyte count persistently higher than 500 to 800/μL ($0.5–0.8\times10^9$/L) on more than 2 CBC measurements, one should send a peripheral blood smear for pathology review, in addition to considering evaluating the child for underlying connective tissue disorders if symptoms exist. Causes of monocytosis that should be considered include infection and, although rare in children, malignancy.

Basophilia is defined as an absolute basophil count higher than 200/μL ($>0.2\times10^9$/L) which could be secondary to inflammatory conditions, hypersensitivity reactions, infections, and occasionally myeloproliferative diseases.

PLATELETS

Platelets are the smallest of the 3 major blood cells. Platelets play a key role in primary hemostasis and circulate at a concentration of approximately 150 to 450×10^3/μL ($150–450\times10^9$/L). Platelet number and normal values do not vary with age. The expected life span of platelets is 7 to 10 days, and they are removed from the circulation by the reticuloendothelial system. (14) An elevated platelet count or thrombocytosis (platelet count, $>450\times10^3$/μL [$>450\times10^9$/L]) can be directly or indirectly associated with acute or chronic inflammation, and platelets are classified as an acute phase reactant. Thrombocytopenia is generally defined as a platelet count less than 100×10^3/μL (100×10^9/L). Patients with thrombocytopenia may be at increased risk for bleeding, and some patients seem more prone to bleeding signs and symptoms than others. Patients with mild (platelet count, $50–100\times10^3$/μL [$50–100\times10^9$/L]) and moderate (platelet count, $20–50\times10^3$/μL [$20–50\times10^9$/L]) thrombocytopenia have less likelihood of spontaneous bleeding compared with patients with severe thrombocytopenia (platelet count, $<20\times10^3$/μL [$<20\times10^9$/L]) in whom bleeding risk is markedly increased.

Platelet disorders are divided into those of platelet number, either increased or decreased (abnormal production, destruction, or consumption), and platelet function, in which platelet number is normal but there is a defect in the platelet's ability to perform its role in hemostasis. Platelets work with von Willebrand factor through adhesion (GPIb-IX-V) and aggregation (GPIIb-IIIa) to bind to the vascular endothelium in the event of vascular damage. (15) Platelet activation and adhesion are the first steps in the development of normal hemostasis. Patients who experience bleeding due to platelet disorders usually present with mucocutaneous bleeding signs, including gum bleeding, epistaxis, and menorrhagia.

ISOLATED PLATELET DISORDERS

After assessment of Hgb, RBC indices, and WBC counts, the next step is to evaluate the platelet count on the CBC.

Table 5. Platelet Parameters in the Pediatric Population

Age	Platelet Count, /μL ($\times10^9$/L) (mean ±1 SD)
Preterm, 27–31 wk	275,000 ± 60,000 (275 ± 60)
Preterm, 32–36 wk	290,000 ± 70,000 (290 ± 70)
Term infants	310,000 ± 68,000 (310 ± 68)
Healthy adult or child	300,000 ± 50,000 (3,000 ± 50)

Table 6. Disorders of Platelets

A. Impaired platelet production (inherited vs acquired causes)		
Inherited Causes		
	Peripheral Smear	Other findings/Associations
Wiskott-Aldrich	Small platelets	Eczema & immunodeficiency
X-linked thrombocytopenia	Small platelets	
MYH-9 related disorders	Döhle bodies `leukocyte inclusions'; Giant platelets	RF, sensorineural hearing loss, cataracts
Thrombocytopenia absent radii	Severe thrombocytopenia newborn' Giant platelets	Absence of the radii; Thumbs present; cow's milk intolerance; IBMFS
CAMT	Severe thrombocytopenia newborn' Giant platelets	Absent/reduced megakaryocytes in BM; IBMFS
Fanconi Anemia	Varies (+/- anemia, leukopenia, thromocytopenia)	Congenital anomalies +/- radial deformities; +/- thumbs absent; IBMFS
Acquired Causes		
Infections	EBV, CMV, HIV, Varicella, Parvo, Hep C	Common viral infections; TORCH in neonates
Infiltration		Metabolic disorders
Malignancy	Peripheral blasts with leukemia	Very sick child, other cytopenia
Liver failure		Decrease TPO-produced in the liver
B. Increased platelet destruction	**Associated with elevated IPF and elevated MPV if adequate bone marrow compensation**	
Acquired Causes-Immune		
Neonatal Alloimmune Thrombocytopenia	Thrombocytopenia early at birth (in utero or at day 1)	Mother usually HPA-; neonate HPA+
Neonatal Autoimmune Thrombocytopenia	Thrombocytopenia on days 3-4 of life	Associated with maternal ITP
Hemolytic Disease of the Newborn		
Immune Thrombocytopenia (ITP)	No other cytopenia	Acute onset-healthy child
Infections	EBV, CMV, HIV, Varicella, Parvo, Hep C	Common viral infections; TORCH in neonates
Evan's Syndrome	Thrombocytopenia and signs of hemolysis	ITP + AIHA
Triggered by autoimmune disorders		SLE, JA, DM-I
Drug induced		Heparin, Valproic acid, Dilantin, others
Aplastic anemia	Pancytopenia	Plt <20,000, Hb <7.0 & ANC <200
Acquired Causes-Non Immune (usually transitory-recovers after treating underlying cause)		
Chronic fetal hypoxia		Newborn period
Maternal Diabetes or hypothyroidism		Newborn period
Pregnancy-induced hypertension		
Intauterine Growth Restriction		
Sepsis/DIC		
HLH		
Sepsis		
Splenic sequestration		Associated with portal hypertension, cyanotic heart disease, infiltration
Destruction/Consumption (TMA)		HUS, aHUS, TTP, hemangioma in Kasabach-Merritt syndrome
Chemotherapy	Likely pancytopenia-depending on agent	Recovers after count nadir
Acquired Causes-Mechanical/Technical		
ECMO		Platelet consumption on circuit
Platelet dumping 'pseudo thrombocytopenia'	Occurs with EDTA tubes 'purple top'	Normalize on citrate
Dilutional		
Massive transfusions		

AIHA5autoimmune hemolytic anemia, aHUS5 atypical hemolytic uremic syndrome, BM5bone marrow, CAMT5congenital amegakaryocytic thrombocytopenia; CMV5cytomegalovirus, DIC5disseminated intravascular coagulation, DM 15diabetes mellitus type 1, EBV5Epstein- Barr virus, ECMO5extracorporeal membrane oxygenation; HIV5human immunodeficiency virus, HLH5hemophagocytic lymphohistiocytosis, HPA5human platelet antigen, IBMFS5inherited bone marrow failure syndrome, IPF 5 immature platelet fraction, ITP5immune thrombocytopenia, JA5juvenile arthritis, MPV5mean platelet volume, SLE5systemic lupus erythematosus, TMA5thrombotic microangiopathy, TORCH, toxoplasmosis, other (such as syphilis, varicella, mumps, parvovirus), rubella, CMV, and HIV, TPO5thrombopoietin, TTP5thrombotic thrombocytopenic purpura.

Figure 10 provides an algorithm to guide evaluation of thrombocytopenia and thrombocytosis; Table 5 contains standard reference ranges, and Table 6 includes common platelet disorders and associated laboratory findings. If the platelet count is 150 to $450 \times 10^3/\mu L$ [150–$450 \times 10^9/L$] and there are no clinical signs or symptoms of bleeding, no

further investigation is needed. A normal platelet count with mucosal bleeding symptoms should be referred to pediatric hematology-oncology for evaluation of a functional platelet disorder. For a platelet count less than $150 \times 10^3/\mu L$ ($<150 \times 10^9/L$), a diagnosis of thrombocytopenia should be considered and needs further investigation. The CBC should be repeated to determine whether the blood draw technique or other laboratory procedure caused low values due to platelet activation, thereby causing pseudothrombocytopenia. If thrombocytopenia persists on CBC repeat, a peripheral blood smear to search for platelet clumping and platelet size should be performed. If no evidence of platelet clumping or morphologic abnormalities is seen on peripheral blood smear, one should assess for bone marrow response to thrombocytopenia with the mean platelet volume or immature platelet fraction.

If the platelet count is higher than $450 \times 10^3/\mu L$ [$>450 \times 10^9$/L], a diagnosis of thrombocytosis is established. Most thrombocytosis in children can be attributed to secondary or reactive causes such as inflammation, infection, and iron deficiency. Patients who have had a splenectomy will also have thrombocytosis. If secondary thrombocytosis is ruled out, primary thrombocytosis such as essential thrombasthenia should be considered. Primary thrombocytosis is extremely rare in children, and, if suspected, a referral is warranted to pediatric hematology-oncology.

Summary

- The identification of abnormal complete blood count (CBC) requires clinicians to use an appropriate set of reference ranges, acknowledging that CBC will vary based on a child's age and sex. (Based on consensus)
- Consensus recommendation now advocates against using race-based CBC reference ranges. (6)
- An evidence-based approach to interpreting the CBC is critical to avoid missing important diagnoses or pursuing unnecessary evaluation and referral. (Based on consensus) (16)

SUGGESTED READINGS

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References and teaching slides for this article can be found at https://doi.org/10.1542/pir.2021-005273.

PIR QUIZ

1. A 9-month-old boy, who is new to your practice, is seen for a health supervision visit. This child is exclusively breast fed and has received no other nutritional supplementation since birth. A screening hemoglobin level is low (10 g/dL [100 g/L]). You order additional laboratory studies, including a complete blood cell count. Which of the following sets of values/results would be most consistent with this clinical presentation.

   A. Mean corpuscular volume (MCV) = 68 μm^3 (68 fL); platelet count = $450 \times 10^3/\mu L$ (450×10^9/L); reticulocytes = 0.5%; red blood cell distribution width (RDW) = 16.5%.
   B. MCV = 90 μm^3 (90 fL); platelet count = $300 \times 10^3/\mu L$ (300×10^9/L); reticulocytes = 1.1%; RDW = 11%.
   C. MCV = 68 μm^3 (68 fL); platelet count = $450 \times 10^3/\mu L$ (450×10^9/L); reticulocytes = 1.1%; RDW = 11%.
   D. MCV = 68 μm^3 (68 fL; platelet count = $300 \times 10^3/\mu L$ (300×10^9/L); reticulocytes = 0.5%; RDW = 11%.
   E. MCV = 90 μm^3 (90 fL; platelet count = $450 \times 10^3/\mu L$ (450×10^9/L); reticulocytes = 0.5%; RDW = 16.5%.

2. You are evaluating a 3-year-old child referred to your office by the local Woman, Infants, and Children (WIC) program for anemia. On obtaining additional history, you learn that this child was born prematurely and had "some kind of intestinal surgery," as indicated by an abdominal scar on physical examination. There are no unusual dietary preferences reported. Repeated laboratory studies show the following results: hemoglobin, 10.0 g/dL (100 g/L); hematocrit, 30.0%; MCV, 105 μm^3 (105 fL); and reticulocytes, 0.7%. A peripheral blood smear shows megaloblasts and hypersegmented neutrophils. Based on this history and the laboratory results, nutritional deficiency of which of the following is the most likely reason for this child's anemia?

   A. Vitamin C.
   B. Iron.
   C. Vitamin B_{12}.
   D. Vitamin D.
   E. Vitamin E.

3. A 15-year-old boy has become increasingly tired/fatigued during the past 3 to 4 weeks. He denies any changes in mood or drug/alcohol use. On physical examination he exhibits cervical adenopathy, mild jaundice, and some hepatosplenomegaly. Laboratory studies confirm the suspected diagnosis of Epstein-Barr virus infection, but the patient is also noted to be anemic. Which of the following best describes the expected characteristics to be seen in the anemia in this patient?

   A. Microcytic with a decreased reticulocyte count.
   B. Microcytic with an increased reticulocyte count.
   C. Normocytic with a decreased reticulocyte count.
   D. Normocytic with an increased reticulocyte count.
   E. Macrocytic with an increased reticulocyte count.

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4. A 2-year-old child is being evaluated for recurrent fevers in association with mouth ulcers and gingivitis. The parents report that she is repeatedly ill with respiratory illnesses but is currently well. She is frequently sent home from the out-of-home child care she attends. She is not taking any long-term medications, she is growing well, and there is no contributory family history. Laboratory studies (complete blood cell count) report the following results: hemoglobin, 12 g/dL (120 g/L); hematocrit, 37%; normal red blood cell indices; platelet count, $370 \times 10^3/\mu L$ (370×10^9/L); white blood cell count, 4,100,000/μL ($4{,}100 \times 10^9$/L); absolute neutrophil count, 700/mL; lymphocyte count, 3,100/μL (3.10×10^9/L); eosinophil count, 100/μL (0.10×10^9/L); monocyte count, 200/μL (0.20×10^9/L). To develop the most appropriate evaluation and treatment plan, these studies should be repeated in which of the following time frames?

   A. 2–4 wk.
   B. 4–6 wk.
   C. 6–8 wk.
   D. 10–12 wk.
   E. 12–16 wk.

5. You follow in your clinic a 7-year-old girl with cerebral palsy (Gross Motor Function Classification System II) and a poorly controlled seizure disorder treated with valproic acid. Falls associated with her seizures result in easy bruising and mucosal bleeding. Laboratory studies report the following results: hemoglobin, 13.2 g/dL (132 g/L); MCV, 90 μm^3 (90 fL); mean corpuscular hemoglobin, 30 pg; reticulocytes, 1%; white blood cell count, 8,500/μL (8.5×10^9/L); neutrophils, 52%; lymphocytes, 40%; eosinophils, 3%; monocytes, 5%; platelet count, $330 \times 10^3/\mu L$ (330×10^9/L). Which of the following is the most likely etiology for her easy bruising and mucosal bleeding?

   A. Autoimmune reaction.
   B. Chronic infection.
   C. Drug reaction.
   D. Functional platelet disorder.
   E. Malignancy.