The Complete Blood Count

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THE COMPLETE BLOOD COUNT (CBC) is one of the more common laboratory tests ordered during the neonatal period. The CBC may be obtained to evaluate for anemia, infection, and thrombocytopenia.[1] The test offers a wealth of clinical information about the hematopoietic system, including erythrocyte, leukocyte, and thrombocyte values. Establishing normal neonatal ranges has been difficult because blood has not been drawn on healthy neonates of similar ages.[2] Reference ranges that consist of the 5th to 95th percentile compiled from various studies have been used to approximate normal neonatal values.[3] A variety of factors such as sample site, timing of the sample, gestational age, and the neonate's degree of health can affect the CBC.[1] Therefore, the astute practitioner must be able to recognize the clues and nuances of the CBC to guide the diagnostic assessment.[4]

HEMATOPOIESIS

Blood cell development begins in the earliest weeks of gestation. Cell differentiation appears to begin from a population of progenitor or stem cells located within the yolk sac, liver, and bone marrow of the developing fetus.[5] The microchemical environment of the developing stem cells determines the differentiation of at least two cell lines: the myloid hematopoietic system and the lymphoid hematopoietic system.[6]

The myloid hematopoietic cell line leads to the proliferation and differentiation of stem cells into the erythroid, myeloid, and megakaryocyte precursors.[7] The erythrocytes, leukocytes, and thrombocytes develop from these precursors.[8] The lymphoid hematopoietic cell line produces the lymphocytes. Lymphocytes follow one of two independent pathways to produce the cells that will become either T lymphocytes or B lymphocytes (Figure 1).

COMPONENTS OF THE CBC

The CBC provides information on the following:[9]

- erythrocyte, or red blood cell (RBC), count
- measure of hemoglobin (Hgb)
- hematocrit (Hct) (percentage)
- mean corpuscular hemoglobin (MCH) measurement
- mean corpuscular hemoglobin concentration (MCHC)
- mean corpuscular volume (MCV)
- leukocyte, or white blood cell (WBC), count
- thrombocyte count
- explanation of cell morphology

Several factors can affect CBC values. Postnatal fluid shifts can alter the hemoglobin and hematocrit levels, and late clamping of the umbilical cord may result in an elevated hematocrit and transitory polycythemia.[5,6,9] Values can vary between sample sites. For example, capillary samples have approximately an 82 percent correlation with venous samples and approximately a 77 percent correlation with arterial samples, with the capillary site having a higher hemoglobin concentration and hematocrit value due to the sludging of RBCs in the low-flow capillaries and transudation of plasma.[10] The sample site must be taken into consideration when the practitioner reviews the CBC because it can impact the intervention. For example, a capillary sample may reveal an elevated hemoglobin level and hematocrit percentage, an indicator of polycythemia. In this situation, an arterial or venous sample would give a more accurate value.[11,12] Neutrophil counts can be affected by the type of delivery the infant experienced and the timing of the sample. Neutrophil values peak at approximately six to eight hours of age in neonates born at >28 weeks gestation.[1]

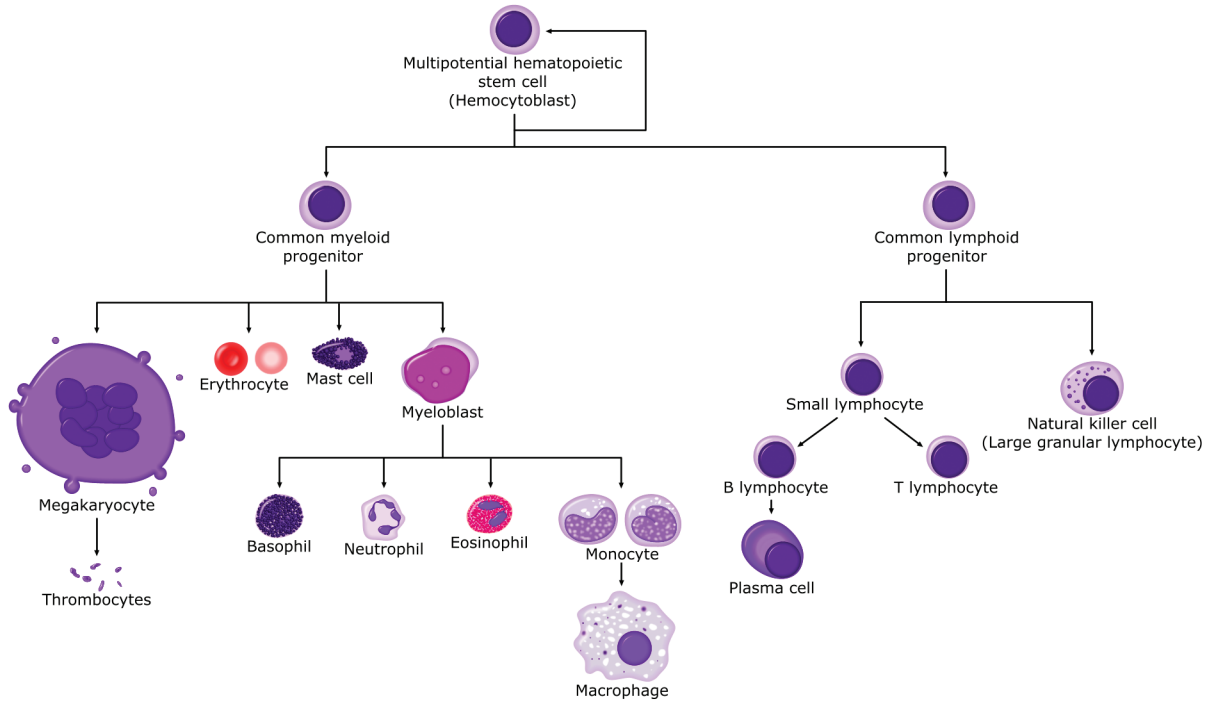
ERYTHROCYTES

Erythrocytes, red blood cells, first appear in the yolk sac during the mesoblastic period; this period begins at approximately two weeks gestation and peaks at approximately six weeks gestation.[6] The RBC count measures the number of circulating erythrocytes. A mature RBC is a nonnucleated, biconcave disc, surrounded by a flexible membrane. Fetal (and neonatal) RBCs differ from adult RBCs in that they are larger in size, have a shorter life span, altered shape and deformability, and they contain a high fetal hemoglobin concentration.[5] RBCs transport oxygen to the organs and tissues; it is the protein, hemoglobin, in erythrocytes that carries oxygen.[10]

The hematocrit is the proportion of blood volume that consists of the RBCs. It is expressed as a percentage on the CBC. Hemoglobin in blood is measured in grams per one deciliter of whole blood and is expressed as g/dL (mmol/L) on the CBC.

Two conditions that can be identified by evaluating the RBC count are anemia and polycythemia. Anemia is a deficiency in the concentration of erythrocytes and hemoglobin in the blood. Neonatal anemia can be caused by acute, chronic, or iatrogenic blood loss; decreased erythrocyte production; increased destruction of erythrocytes, as with hemolysis; or shortened erythrocyte survival.[10] Polycythemia is most commonly defined as a venous hematocrit greater than 65 percent.[11] Because RBC concentration directly impacts blood viscosity, neonates with polycythemia may exhibit symptoms as a result of increased viscosity. They may

FIGURE 1 ■ Hematopoietic stem cells give rise to two major progenitor cell lineages, myeloid and lymphoid progenitors.



Courtesy of Mikael Häggström.

TABLE 1 ■ Erythrocyte and Platelet Reference Ranges in Term and Preterm Neonates during the First 72 Hours of Life

Age	Hgb (g/dL)*	Hct (%)*	RBC (mm^3)	MCV (μL^3)	MCH (%)	MCHC (%)	Platelets ($1,000/mm^3$)†
Term							310
24 hours	18.4	58	5.8	108	35	33	
72 hours	17.8	55	5.6	99	33	32.5	
Preterm							290
34 weeks	15	47	4.4	118	38	32	
28 weeks	14.5	45	4	120	40	31	
* (±1 SD)	†mean						

Adapted from: Klaus, M. H., & Fanaroff, A. A. (Eds.). (2001). Appendix C-4. In *Care of the high-risk neonate* (5th ed., p. 574). Philadelphia: Saunders; Askin, D. F. (2004). Appendix A-1. In *Infection in the neonate: A comprehensive guide to assessment, management, and nursing care* (p. 181). Santa Rosa, CA: NICU Ink.

TABLE 2 ■ Types of Leukocytes

Granulocytes	Contain granules in cytoplasm
Neutrophils	Segmented and band forms
Eosinophils	
Basophils	
Agranulocytes	Do not contain granules in cytoplasm
Lymphocytes	
Monocytes	

be plethoric with occasional cyanosis or may exhibit neurologic symptoms of lethargy, irritability, and hypotonia.[13]

There are other indices that can provide estimates of the average size of the erythrocytes and the average concentration and quantity of hemoglobin in the erythrocytes. These indices can be measured directly or calculated electronically using modern hematology analyzers. They can be useful in further classifying anemia according to the hemoglobin quantity in the RBCs or the size of the RBCs or in identifying the pathologic process causing the anemia. The erythrocyte indices include the MCV, the MCHC, and the MCH. The MCV measures the average size of circulating erythrocytes. It can help to quantify anemia as microcytic (small cells) or macrocytic (large cells). An elevated MCV is seen with hyperviscosity/polycythemia and also in anemia caused by folate or vitamin B_{12} deficiency. The MCHC measures the hemoglobin concentration in a given volume of red blood cells. The RBCs can be described as normochromic, hypochromic, or hyperchromic, depending on their color, which is determined by the amount of hemoglobin present in the RBC. The MCH measures the average amount of hemoglobin per RBC in a sample of blood

TABLE 3 ■ Leukocyte Reference Ranges in Term and Preterm Neonates during the First 72 Hours of Life (10^3 cells/μL)

Age	Total WBC	Neutrophils	Bands	Lymphocytes	Monocytes	Eosinophils	Basophils
Term							
Birth	10–26	5–13	0.4–1.8	3.5–8.5	0.7–1.5	0.2–2	0–1
12 hours	13.5–31	9–18	0.4–2	3–7	1–2	0.2–2	0–1
72 hours	5–14.5	2–7	0.2–0.4	2–5	0.5–1	0.2–1	0–1
Preterm							
Birth	5–19	2–9	0.2–2.4	2.5–6	0.3–1	0.1–0.7	0–1
12 hours	5–21	3–11	0.2–2.4	1.5–5	0.3–1.3	0.1–1.1	0–1
72 hours	5–14	3–7	0.2–0.6	1.5–4	0.3–1.2	0.2–1.1	0–1

Adapted from: Klaus, M. H., & Fanaroff, A. A. (Eds.). (2001). Appendix C-7. In *Care of the high-risk neonate* (5th ed., p. 577). Philadelphia: Saunders; Askin, D. (2004). Appendix C-1. In *Infection in the neonate: A comprehensive guide to assessment, management, and nursing care* (p. 187). Santa Rosa, CA: NICU Ink.

(Table 1).[14] The MCHC can be used to identify anemia due to an acute or chronic blood loss.[5] Many changes in erythrocyte morphology can be identified using the CBC; a few include anisocytosis (variation in cell size), macrocytosis, microcytosis, schistocytes (fragmented cells), and spherocytes (rounded cells). Anisocytosis can be seen on a peripheral blood smear and may indicate a normal variation in the size of the RBCs. Macrocytosis is a condition of abnormally large-sized mature RBCs and may be used in the classification of anemias. Microcytosis describes RBCs of small size and may be seen with anemias caused by chronic blood loss or an iron deficiency.[5] Schistocytes or fragmented red blood cells are indicative of intravascular hemolysis and can also be seen in cases of disseminated intravascular coagulation (DIC). Spherocytes, or rounded red blood cells, may indicate congenital spherocytosis, a condition in which the red blood cell lacks a protein critical to the cell membrane. Without this protein, red blood cells maintain a rounded rather than spherical shape.[15]

LEUKOCYTES

Leukocytes, or WBCs, are the body's main defense against invading organisms. Leukocyte formation begins in the liver at approximately 5 weeks gestation.[16] By approximately 20 weeks gestation, the bone marrow becomes the primary site of leukocyte hematopoiesis.[17] Leukocytes may be classified as granulocytes or agranulocytes, depending on the presence of granules in the cytoplasm (Table 2). The three types of granulocytes are the neutrophils, eosinophils, and basophils. These cells are the most active in defending the body, with the neutrophils having the primary role. Neutrophils are phagocytic cells capable of recognizing, ingesting, and digesting foreign particles; they are generally the first to arrive at the infection site.[18] The neutrophil progresses through six stages of development before it reaches a mature state. These stages are the myeloblast, promyelocyte, myelocyte, metamyelocyte, band, and finally the polymorphonuclear neutrophil or segmented mature neutrophil.[19] The release of immature neutrophils from the bone marrow storage pool into the bloodstream is not fully understood. It is thought that certain substances regulate the production and movement of the neutrophils.[20,21]

When mature neutrophils leave the storage pool and move into the bloodstream, approximately half circulate freely in the bloodstream, constituting the circulating pool. The remainder adhere to the vessel walls as the marginating pool.[19] The neutrophils move constantly between the circulating pool and the marginating pool. Neutrophils circulate in the bloodstream for about 6–8 hours before they migrate to the tissues, where they can live for an additional 24 hours.[22] A small number of bands, immature neutrophils, are normally released into the bloodstream with the mature neutrophils. If these circulating cells cannot meet the body's demand and the storage pool is depleted, more bands and other immature cells are released from the storage pool into the bloodstream.

Mature eosinophils have a bi-lobed nucleus with distinctive granules in the cytoplasm. They

TABLE 4 ■ Calculating WBC Indices

Neutrophil Index	Calculation
Corrected WBC	(Total WBC × 100) ÷ (total NRBC + 100)
ANC	(% segmented neutrophils + immature neutrophils*) × WBC
I:T ratio	% immature neutrophils ÷ % mature + immature neutrophils*
I:M ratio	% immature neutrophils* ÷ % mature neutrophils
B:S ratio	Bands ÷ mature neutrophils

*Immature neutrophils = bands, metamyelocytes, and myelocytes.

Adapted from: Manroe, B. L., Weinberg, A. G., & Rosenfeld, C. R. (1979). The neonatal blood count in health and disease, Part 1: Reference values for neutrophilic cells. *The Journal of Pediatrics, 95,* 89–98; Edwards, M. E. (2006). Postnatal bacterial infections, Part 2. In *Neonatal-perinatal medicine: Diseases of the fetus and infant* (8th ed., p. 796). Philadelphia: Mosby Elsevier.

TABLE 5 ■ Reference Ranges for ANC and I:T Neutrophil Indices in the Neonate during the First 72 Hours of Age

	ANC*	I:T*
Age		
Birth	1,800–5,400	<0.16
12 hours	7,800–14,400	<0.16
24 hours	7,200–12,600	<0.13
72 hours	1,800–7,000	<0.13

*Index per cubic mm.

Adapted from: Manroe, B. L., Weinberg, A. G., & Rosenfeld, C. R. (1979). The neonatal blood count in health and disease, Part 1: Reference values for neutrophilic cells. *The Journal of Pediatrics, 95,* 89–98; Edwards, M. E. (2006). Postnatal bacterial infections, Part 2. In *Neonatal-perinatal medicine: Diseases of the fetus and infant* (8th ed., p. 796). Philadelphia: Mosby Elsevier.

have immuno-enhancing and immunosuppressive functions and play a role in selective tumor response, helminthic (parasitic) infections, and allergies.

Mature basophils have a bi-lobed nucleus with metachromatic granules in the cytoplasm that contain heparin, histamine, and several other proteins.[16] Basophils mature and differentiate in the bone marrow before they are released into the circulation. They function in chemotaxis; phagocytosis; granule release of histamine, peri-oxidase, and heparin; and in factor synthesis. Basophils also participate in hypersensitivity reactions.[9]

The two types of agranulocytes are lymphocytes and monocytes. Lymphocytes function in the immune response. There are three types of lymphocytes: B cells, T cells, and the natural killer (NK) cells. Lymphocytes are small, round cells with blue-black nuclei after staining; they are not phagocytes, but are migratory cells.[23]

Monocytes are large cells with a horseshoe-shaped nucleus. They are specialized phagocytes that are able to release cellular mediators. They can circulate in the bloodstream for approximately eight hours, after which they migrate to the tissues to become macrophages. They defend against intracellular parasites; remove cellular debris; participate in iron metabolism; present antigens to lymphocytes during an immune response; and secrete various enzymes, factors, and interferons.[9,16,24]

Abnormalities of the WBCs

The CBC measures the number and types of circulating leukocytes. The differential count identifies the types of leukocytes according to their morphology and categorizes the types as a percentage value on the CBC (Table 3).[12] Leukocytosis refers to an elevated WBC count; it may be seen with infections, leukemias, or leukemoid reactions. If the WBC count is determined using an automated cell analyzer, it can be falsely elevated because this machine frequently counts/misidentifies nucleated red blood cells (NRBCs) as WBCs because they are similar in size. Routinely, this is corrected in the laboratory by a manual count of all the cells on a peripheral smear; however, it can also be calculated (Table 4). Leukopenia refers to a decreased WBC count; it can be seen with viral or bacterial infections as well as in infants born to women with pregnancy-induced hypertension (PIH).[25]

Morphologic or degenerative changes that may be seen in granulocytes include vacuoles (visible openings), Dohle bodies (cytoplasmic inclusions), and toxic granulation (larger-than-normal granules). These are nonspecific changes that can be found in approximately 63 percent of neonates with confirmed sepsis.[12]

Neutrophilia and neutropenia can be identified using the CBC. In 1979, Manroe and colleagues from the University of Texas Southern Medical School published reference values for blood neutrophil concentrations.[26] This landmark study has been used as a baseline to identify and study neutrophil ranges during the first 60 hours after birth. Neutrophilia is an increase in the number of neutrophils in the bloodstream and can result from inflammation, certain malignancies, or the presence of corticosteroid

TABLE 6 ■ Terms Used to Describe Accuracy and Reliability of Laboratory Tests

Term	Definition
Sensitivity	The ability of a test to correctly identify those infants who truly are infected; the percentage of patients with infection who have an abnormal test
Specificity	The ability of a test to correctly identify those infants who do not have infections; the percentage of patients without infection who have a normal test
Positive predictive value	The percentage of positive tests that are true positive (i. e., the infant has an infection); if the test is abnormal (positive), the percentage of infants with infection
Negative predictive value	The percentage of negative tests that are true negative (i. e., the infant does not have an infection); if the test is normal, the percentage of infants with no infection

Adapted from: Pincus, M. R. (1996). Interpreting laboratory results: Reference values and decision making. In J. B. Henry (Ed.), *Clinical diagnosis and management by laboratory methods* (19th ed., p. 76). Philadelphia: Saunders; Weinberg, G. A. & Powell, K. R. (2001). Laboratory aids for diagnosis of neonatal sepsis. In J. Remington and J. Klein (Eds.), *Infectious diseases of the fetus and newborn infant* (5th ed., pp. 1327–1344). Philadelphia: Saunders.

drugs.[27] Neutropenia is a decrease in the number of neutrophils in the bloodstream and can result from infection, impaired bone marrow production, or abnormal distribution. Neutropenia is more predictive of neonatal sepsis than is neutrophilia, but it can also be associated with PIH, birth asphyxia, intrauterine growth restriction, Rh hemolytic disease, or periventricular hemorrhage. Neutropenia associated with PIH is a result of diminished production and generally resolves in three to five days.[25,28]

Eosinophilia is frequently overlooked because its significance and causative factors are not clearly understood. Eosinophilia may be caused by infection, antibiotics, exposure to antigens in parenteral nutrition, catheters, and blood products; it may also be seen in preterm infants experiencing an anabolic growth period.[27]

Calculated White Blood Cell Indices

The indices that can be calculated from the CBC include the WBC count correction, the absolute neutrophil count (ANC), the immature-to-total neutrophil ratio (I:T), the immature-to-mature neutrophil ratio (I:M), and the band-to-segmented neutrophil ratio (B:S) (see Table 4).[12] An increased percentage of bands (and other immature cells) on the CBC is known as a left shift (see Table 4).[12] This term originated when lab reports were written by hand: the less mature neutrophil forms were written first on the left-hand side of the laboratory report. The neutrophil indices may be useful as predictors of neonatal sepsis. The ANC is a measure of the number of neutrophils present in the CBC specimen. A decreased ANC is known as neutropenia, it is a more accurate predictor of an infection in the neonate than neutrophilia. Neutropenia may reflect a depletion of the neutrophil storage pool and be indicative of a bacterial infection. Neutrophilia is a high neutrophil count. It is less common in neonates and may be seen with asymptomatic hypoglycemia, oxytocin administration, and meconium aspiration syndrome.[12] The I:T ratio is a measure of the immature neutrophils compared to the total neutrophils. It can be used to identify a left shift. This measurement has emerged as a frequent indicator of neonatal sepsis with a high sensitivity, but a low specificity and predictive value.[29] An I:T ratio >0.3 is suspicious for infection (Table 5, Table 6, Case Review).[12] The I:M ratio can be used to identify a left shift, as can the B:S ratio.

THROMBOCYTES

Thrombocytes, or platelets, are produced in the bone marrow by polyploidy cells called megakaryocytes. Megakaryocytes become giant cells and undergo a process of fragmentation that creates approximately 1,000 platelets/megakaryocyte. Platelets are tiny, 1–4 microns in size. They are disc-shaped, noncellular, anuclear, containing cytoplasmic granules and can survive for approximately nine to ten days in the bloodstream.[30] The major function of platelets is to promote primary hemostasis. During a healthy state, platelets circulate in the bloodstream without adhering to the walls of blood vessels or other cells.[31] When the endothelial lining of the blood vessel becomes injured, platelets are activated. In response to injury, they transform their shape, adhering to and aggregating at the injury site to form a primary hemostatic plug.[32]

Platelet Abnormalities

Thrombocytopenia and thrombocytosis can be identified on a CBC (see Table 1). Thrombocytopenia is a condition of reduced platelets.[33] It is one of the most common hematologic problems in sick neonates.[34] It can be caused by decreased production or by increased destruction, sequestration, or loss as a result of many conditions. The differential diagnosis includes bacterial and viral sepsis, hypoxia, DIC, necrotizing enterocolitis, persistent pulmonary hypertension of the newborn, erythroblastosis fetalis, polycythemia, congenital infections, congenital anomalies/syndromes, neonatal alloimmune thrombocytopenia, maternal immune thrombocytopenic purpura, and preeclampsia.[33,34] Depending on the severity of the thrombocytopenia, the symptoms may vary, but can include petechiae; purpura; gastrointestinal, cutaneous, and mucosal bleeding; hematuria; and central nervous system hemorrhage.[30]

Neonates rarely display signs of thrombocytosis.[13] Thrombocytosis may be physiologic or associated with infection, inflammation, iron deficiency, medications such as the cephalosporins, asplenia syndrome, vitamin E deficiency, congenital neoplasms, Down syndrome, or congenital adrenal hyperplasia.[13,35]

Neonatal Case Presentation

A term, female infant was delivered after an uncomplicated pregnancy. A CBC was obtained due to hypothermia. Results were: Hgb 18 g/dL; Hct 54%, WBC count 5.9 × 10^3/μL, differential—30% neutrophils, 20% bands, 25% lymphocytes, 10% monocytes, 3% eosinophils, 2% basophils; platelet count 150,000/mm^3.

Calculated Value		Question
ANC = (30% + 20%) × (5.9 × 10^3) = (0.30 + 0.20) × (5.9 × 10^3) = 0.5 × 5,900 = 2,950		Is the ANC normal?
I:T ratio	= $\frac{20}{30 + 20}$ = $\frac{20}{50}$ = 0.4	Is the immature to total (I:T) leukocyte ratio normal?
I:M ratio	= $\frac{20}{30}$ = 0.666, rounds to 0.67	Is the immature to mature (I:M) ratio normal?
B:S ratio	= $\frac{20}{30}$ = 0.666, rounds to 0.67	Is the band to segmented neutrophil (B:S) normal?

The Hct and Hgb are normal. The WBC and platelet counts are low. The ANC is normal. The I:T, I:M, and B:S ratios are elevated. This neonate would need a sepsis evaluation and a repeat CBC to follow up on these abnormal values.

SUMMARY

The CBC is commonly ordered during the neonatal period. It not only provides absolute values, but it can also identify changes in the cellular morphology of the erythrocytes, leukocytes, and thrombocytes. Generally, the CBC is an easy test to obtain in the nursery from a capillary, venous, or arterial sample. The results can be affected by a variety of factors, however, and normal ranges may differ between laboratories. In view of the many benefits and oddities of the CBC, practitioners must assess the maternal history and the individual neonate's perinatal course, state of health, timing of sample, and sample site to interpret the CBC results so that they can guide clinical intervention.

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