How to Interpret and Pursue an Abnormal Complete Blood Cell Count in Adults

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A complete blood cell count (CBC) is one of the most common laboratory tests in medicine. For example, at our institution alone, approximately 1800 CBCs are ordered every day, and 10% to 20% of results are reported as abnormal. Therefore, it is in every clinician's interest to have some understanding of the specific test basics as well as a structured action plan when confronted with abnormal CBC results. In this article, we provide practical diagnostic algorithms that address frequently encountered conditions associated with CBC abnormalities including anemia, thrombocytopenia, leukopenia, polycythemia, thrombocytosis, and leukocytosis. The objective is to help the nonhematologist recognize when a subspecialty consultation is reasonable and when it may be circumvented, thus allowing a cost-effective and intellectually rewarding practice.

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ACD = anemia of chronic disease; ANC = absolute neutrophil count; CBC = complete blood cell count; CML = chronic myeloid leukemia; ET = essential thrombocythemia; FISH = fluorescence in situ hybridization; Hct = hematocrit; HES = hypereosinophilic syndrome; Hgb = hemoglobin; HIV = human immunodeficiency virus; IDA = iron deficiency anemia; ITP = idiopathic thrombocytopenic purpura; LDH = lactate dehydrogenase; LGL = large granular lymphocyte; MCV = mean corpuscular volume; MDS = myelodysplastic syndrome; PA = pernicious anemia; PBS = peripheral blood smear; PT = primary thrombocytosis; PV = polycythemia vera; RBC = red blood cell; RCM = RBC mass; RT = reactive thrombocytosis; TCR = T-cell receptor; TTP/HUS = thrombotic thrombocytopenic purpura/hemolytic uremic syndrome; WBC = white blood cell

Circulating blood cells, including red blood cells (RBCs), white blood cells (WBCs), and platelets, are counted and sized electronically by modern instruments.[1,2] One such instrument, the Coulter counter, generates an electrical pulse when a blood cell passes through a small aperture surrounded by electrodes. Each electrical pulse represents an individual cell, and the pulse height indicates the cell volume. Therefore, the electronic counter not only registers the total cell count but also estimates the average cell volume and the variation in cell size. In the context of RBCs, for example, these measurements are referred to as the mean corpuscular volume (MCV) and the RBC distribution width, respectively. Modern electronic counters are also capable of multimodal assessment of cell size and content, thus providing additional information about the various categories of WBCs including neutrophils, lymphocytes, monocytes, eosinophils, and basophils (ie, 5-part differential).

Two other "measured variables" of the complete blood cell count (CBC) are hemoglobin (Hgb) and hematocrit (Hct). Both provide equivalent information, approximately conveyed by the RBC count, and are interchangeable.[3,4] The Hgb is computed by a spectrophotometer after RBCs are lysed in a given volume of blood and the Hgb is chemically converted into a stable pigment. The Hct is determined by a microhematocrit centrifuge and represents the percentage of a given volume of whole blood that is occupied by packed RBCs.[5,6] However, Hct also can be calculated by multiplying the RBC count and the MCV. Other "calculated" variables in the CBC include the mean corpuscular Hgb content (Hgb × 1/RBC count) and mean corpuscular Hgb concentration (Hgb × 1/Hct); these 2 calculated values are rarely used in routine clinical practice.

For practical purposes, the variables to focus on when examining the CBC are Hgb (as a general indicator of anemia or polycythemia), MCV (a key parameter for the classification of anemias), RBC distribution width (a relatively useful parameter in the differential diagnosis of anemia), RBC count (an increased RBC count associated with anemia is characteristic in the thalassemia trait), platelet count (to detect either thrombocytopenia or thrombocythemia), and WBC count with differential (usually gives important clues for the diagnosis of acute leukemia and chronic lymphoid or myeloid disorders as well as for the presence of leukopenia and neutropenia). Furthermore, in patients with an abnormal WBC count, the clinician should immediately ask which WBC type is affected: neutrophils, lymphocytes, monocytes, eosinophils, or basophils. In this regard, the machine-derived 5-part differential should be confirmed by the human eye (ie, peripheral blood smear [PBS] examination) before it is acted on.

Finally, an "abnormal" CBC should be interpreted within the context of an individual's baseline value because up to 5% of the general population without disease may display laboratory values outside the statistically assigned "normal" reference range[7] (Table 1[8,9]). Likewise, an individual may display a substantial change from his or her baseline (ie, personal normal) without violating the "normal" reference range. Similarly, differences in the CBC based on race and sex should be considered when interpreting results. In general, RBC-associated measurements are lower and platelet counts are higher in women compared

TABLE 1. **Reference Ranges of Complete Blood Cell Count in Adult White Persons and Persons of African Ancestry***

Variable	White		African	
	Male	Female	Male	Female
Hemoglobin[9] (g/dL)	12.7-17.0 (13.5-17.5)	11.6-15.6 (12.0-15.5)	11.3-16.4	10.5-14.7
RBCs[9] ($\times 10^{12}$/L)	4.0-5.6 (4.3-5.7)	3.8-5.2 (3.9-5.0)	3.8-5.7	3.6-5.2
Mean corpuscular volume[9] (fL)	81.2-101.4 (81.2-95.1)	81.1-99.8 (81.6-98.3)	77.4-103.7	74.2-100.9
RBC distribution width (%)	(11.8-15.6)	(11.9-15.5)		
Platelets[8] ($\times 10^9$/L)	143-332 (150-450)	169-358 (150-450)	115-290	125-342
WBCs[8] ($\times 10^9$/L)	3.6-9.2 (3.5-10.5)	3.5-10.8 (3.5-10.5)	2.8-7.2	3.2-7.8
Neutrophils[8] ($\times 10^9$/L)	1.7-6.1 (1.7-7.0)	1.7-7.5 (1.7-7.0)	0.9-4.2	1.3-4.2
Lymphocytes[8] ($\times 10^9$/L)	1.0-2.9 (0.9-2.9)	0.95-3.3 (0.9-2.9)	1.0-3.2	1.1-3.6
Monocytes[8] ($\times 10^9$/L)	0.18-0.62 (0.3-0.9)	0.14-0.61 (0.3-0.9)	0.15-0.58	0.15-0.39
Eosinophils[8] ($\times 10^9$/L)	0.03-0.48 (0.05-0.50)	0.04-0.44 (0.05-0.50)	0.02-0.79	0.02-0.41
Basophils ($\times 10^9$/L)	(0-0.3)	(0-0.3)		

*Abstracted from population-based studies from Bain[8] and NHANES-II.[9] Mayo Clinic normal values, based primarily on white subjects, are in parentheses for comparison. RBC = red blood cell; WBC = white blood cell.

with men, and persons of African ancestry display significantly lower Hgb, WBC, neutrophil, and platelet counts than white persons.[8,9]

ANEMIA

The first step in approaching anemia is to classify the process as microcytic (MCV, <80 fL), normocytic (MCV, 80-100 fL), or macrocytic (MCV, >100 fL).[10,11] This exercise markedly narrows the differential diagnosis that needs to be considered in each patient. Also, we strongly recommend obtaining a PBS during the initial evaluation of anemia, regardless of subtype. A PBS substantially enhances the initial process of differential diagnosis and provides guidance for further testing.

MICROCYTIC ANEMIA
The 3 major diagnostic possibilities for microcytic anemia are iron deficiency anemia (IDA), thalassemia, and anemia of chronic disease (ACD).[10,11] A fourth possibility, sideroblastic anemia presenting with microcytosis, is not prevalent enough for routine consideration.[12] Clues from the CBC and PBS for the differential diagnosis of microcytic anemia are outlined in Table 2. Since the most common of the microcytic anemias is IDA, we recommend determination of the serum ferritin level as the initial step

for all patients with microcytic anemia (Figure 1).[13] A low serum ferritin level is diagnostic of IDA. Similarly, contrary to current dogma regarding acute phase reaction, a diagnosis of IDA is unlikely in the presence of a persistently normal or elevated serum ferritin level.[14] In general, we do not recommend either other serum iron studies (serum iron, total iron-binding capacity, transferrin saturation) or bone marrow biopsy for evaluation of IDA.[10,14]

If the serum ferritin level is normal, the next step is to determine whether the microcytosis is new (Figure 1). In patients with chronic microcytosis, a diagnosis of thalassemia should be considered, and Hgb electrophoresis should be ordered as the initial test.[15] However, we underscore that Hgb electrophoresis does not always detect the presence of thalassemia and that a hematology consultation may be necessary for accurate interpretation of test results. In general, Hgb electrophoresis results are normal in the α-thalassemia trait and abnormal in the β-thalassemia trait as well as in other thalassemic syndromes.[15] Furthermore, during the interpretation of Hgb electrophoresis, one must remember that concomitant IDA may mask the typical abnormality seen in the β-thalassemia trait, which is an increase in Hgb A_2 ($\alpha_2\delta_2$) level from the normal value of 2% to a value of 3% to 6%.[15]

Acquired microcytic anemia that is not IDA is indicative of an underlying systemic disease and is labeled opera-

TABLE 2. **Clues From CBC and PBS in the Differential Diagnosis of Anemias***

Category of anemia	Differential diagnosis	CBC clues	PBS clues
Microcytic	Iron deficiency anemia	Increased RDW Thrombocytosis	Anisocytosis Poikilocytosis Elliptocytosis
	Thalassemia	Normal or elevated RBC count Normal or elevated RDW	Polychromasia Target cells Basophilic stippling
	Anemia of chronic disease	Normal RDW	Unremarkable (typically) Rouleaux formation (CD) Myelophthisis (MMM)†
Normocytic	Bleeding	Usually unremarkable	Polychromasia
	Nutritional anemia	Increased RDW	Anisocytosis Dimorphic RBCs
	Anemia of renal insufficiency	Normal RDW	Usually unremarkable
	Hemolysis	Normal or elevated RDW Thrombocytosis	Polychromasia Spherocytes Schistocytes Bite cells
	Anemia of chronic disease	Normal RDW	Unremarkable
	A primary bone marrow disorder	Increased RDW Other cytopenias Monocytosis Leukocytosis Thrombocytosis Abnormal differential	Dimorphic RBCs (MDS) Pseudo Pelger-Huët anomaly (MDS) Oval macrocytes (MDS) Myelophthisis (MMM)† Rouleaux (myeloma) Blasts (acute leukemia) Presence of abnormal cells
Macrocytic	Drug-induced	Increased RDW Marked or mild macrocytosis	Oval macrocytes
	Nutritional	Increased RDW Marked or mild macrocytosis	Oval macrocytes Hypersegmented neutrophils
	MDS or other bone marrow disorder	Increased RDW	Dimorphic RBCs Pseudo Pelger-Huët anomaly cells Oval macrocytes
	Liver disease, alcohol use	Normal RDW Thrombocytopenia	Round macrocytes Target cells
	Hypothyroidism	Normal RDW	Round macrocytes
	Hemolysis	Normal or elevated RDW	Polychromasia

*CBC = complete blood cell count; CD = Casteleman disease; MDS = myelodysplastic syndrome; MMM = myelofibrosis with myeloid metaplasia; PBS = peripheral blood smear; RBC = red blood cell; RDW = RBC distribution width.
†Myelophthisis implies the presence of nucleated RBCs, immature myeloid cells, and tear-drop–shaped RBCs.

tionally as microcytic ACD.[16,17] Both usual and unusual systemic disease may accompany microcytic ACD (Figure 1).[18] Further laboratory investigation in this instance as well as the need for a hematology consultation is dictated by patient history and findings from both the physical examination and the PBS.

NORMOCYTIC ANEMIA

The first step in approaching normocytic anemia is to exclude potentially treatable causes from the standpoint of anemia, including bleeding, nutritional anemia, anemia of renal insufficiency,[19] and hemolysis (Figure 2). Clues from the CBC and PBS for each of these categories are listed in Table 2. Patient history is key in implicating bleeding as a cause of anemia, and a fecal occult blood test can be ordered if indicated. Regarding nutritional anemia, it should be noted that both iron and vitamin B_{12}/folate deficiencies are possible causes of "normocytic" anemia, de-

spite their usual association with microcytic and macrocytic anemia, respectively.[13,20] Anemia of renal insufficiency is addressed easily by checking the serum creatinine level. Hemolytic anemia is usually normocytic but can be macrocytic if accompanied by marked reticulocytosis.

Initial laboratory tests that should be ordered when hemolysis is suspected and/or to exclude the possibility of active hemolysis include serum levels of haptoglobin, lactate dehydrogenase (LDH), and indirect bilirubin as well as reticulocyte count and the PBS (Figure 2).[21,22] In general, active hemolysis is suspected if a low haptoglobin level is associated with increased LDH, indirect bilirubin, or reticulocyte count. The differential diagnosis of a normocytic anemia that is not linked to bleeding, nutrition, renal insufficiency, or hemolysis is either normocytic ACD or a primary bone marrow disorder.[17] Patient history and PBS results provide the most helpful information in distinguishing the two (Table 2; Figure 2).
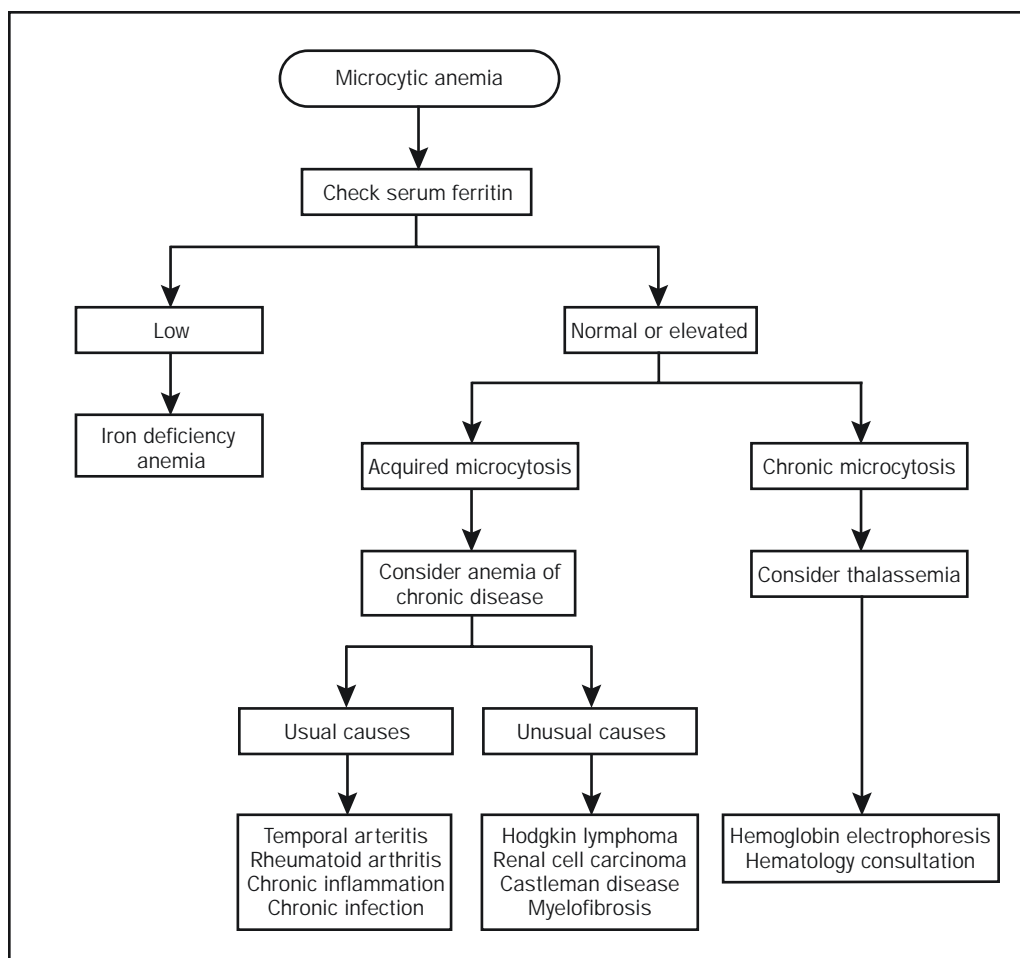
FIGURE 1. Diagnostic algorithm for microcytic anemia.

In general, in patients with normocytic anemia, a hematology consultation may be unnecessary if the patient history, the initial laboratory test results described previously, and the PBS results are consistent with nutritional anemia, anemia of renal insufficiency, or normocytic ACD. Furthermore, some PBS results may dictate the ordering of additional laboratory tests without waiting for approval from a hematologist: (1) a Coombs test and if results are negative, an osmotic fragility test for patients with spherocytosis and (2) coagulation, haptoglobin, and LDH tests for patients with schistocytosis (Figure 2). Similarly, a urinary hemosiderin test is extremely helpful if valvular hemolysis is suspected. All other scenarios require a hematology consultation. Finally, the possibility of drug-induced hemolysis always must be considered.[21]

MACROCYTIC ANEMIA
Use of certain drugs (eg, hydroxyurea, zidovudine) and alcohol consumption are notoriously associated with mac-

rocytosis and should be first considerations during evaluation of macrocytic anemia (Figure 3).[23,24] The next step is to rule out nutritional causes (B_{12} or folate deficiency); we prefer to use serum homocysteine for initial screening because of its higher test sensitivity.[20,25] However, we advocate concomitant determination of the serum B_{12} level to safeguard against laboratory error in view of the dire clinical consequences associated with vitamin B_{12} deficiency (Figure 3). If 1 of the 2 tests has abnormal results, the serum methylmalonic acid level should be checked; an increased level strongly suggests B_{12} deficiency.

In patients with vitamin B_{12} deficiency, the next step is to screen for the presence of intrinsic factor antibodies[26,27]; if present, a working diagnosis of pernicious anemia (PA) is made. Otherwise, the Schilling test is performed to differentiate PA from primary intestinal malabsorptive disorders.[27,28] Further investigation of macrocytic anemia that is neither drug-induced nor nutritional is simplified by subcategorizing the process into either a marked (MCV,
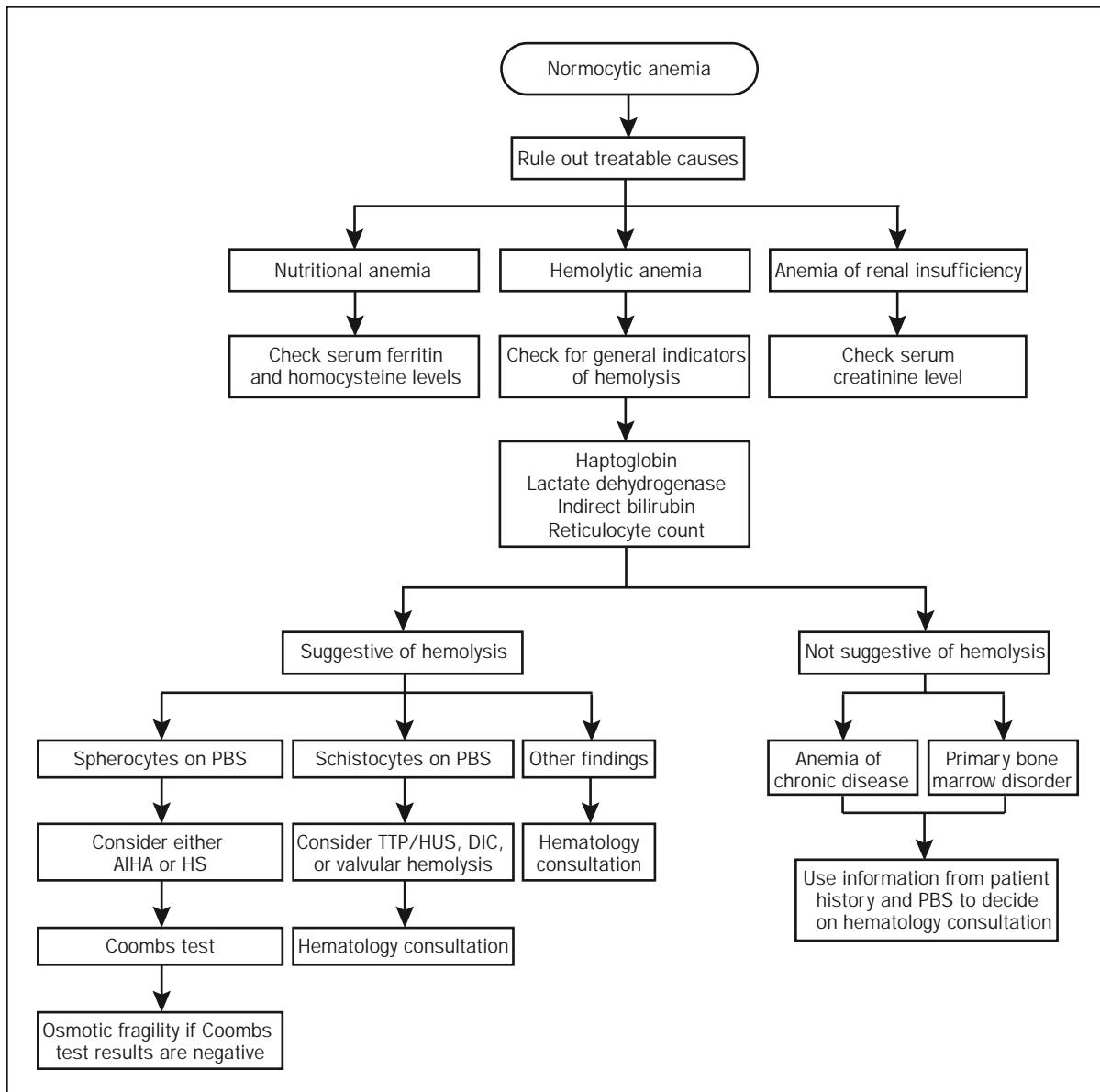
FIGURE 2. Diagnostic algorithm for normocytic anemia. AIHA = autoimmune hemolytic anemia; DIC = disseminated intravascular coagulation; HS = hereditary spherocytosis; PBS = peripheral blood smear; TTP/HUS = thrombotic thrombocytopenic purpura/ hemolytic uremic syndrome.

>110 fL) or mild (MCV, 100-110 fL) subtype. In this instance, markedly macrocytic anemia is almost always associated with primary bone marrow disease, whereas mildly macrocytic anemia also can be associated with more benign conditions (Figure 3).[29,30]

THROMBOCYTOPENIA

The first step in treating thrombocytopenia is to exclude the possibility of spurious thrombocytopenia caused by EDTA-induced platelet clumping (Figure 4).[31] The situation is clarified by either examining the PBS or repeating the CBC using sodium citrate as an anticoagulant. Another important point to consider before starting a costly search for disease is the fact that healthy women may experience mild to moderate thrombocytopenia (platelets, 75-150 × 10^9/L) during pregnancy, and such incidental thrombocytopenia of pregnancy requires no further investigation.[32]

The second step in treating patients with thrombocytopenia is to always consider the possibility of thrombotic

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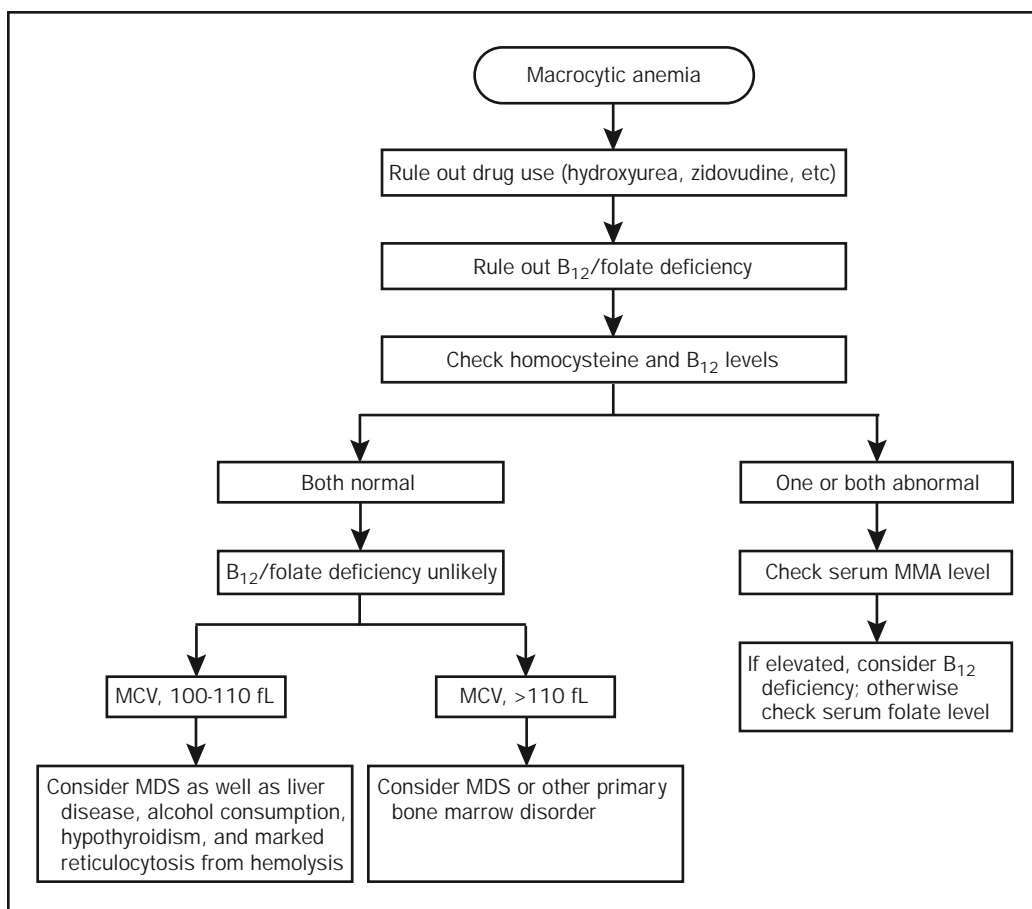
FIGURE 3. Diagnostic algorithm for macrocytic anemia. MCV = mean corpuscular volume; MDS = myelodysplastic syndrome; MMA = methylmalonic acid.

thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS) because of the urgency for specific therapy for these diagnoses (ie, plasma apheresis).[33,34] This is why we recommend PBS (to look for schistocytes); serum levels of haptoglobin and LDH (to assess for concomitant hemolysis) and creatinine; and coagulation tests including plasma levels of D-dimer, in most instances of thrombocytopenia. Both TTP/HUS and disseminated intravascular coagulation are characterized by microangiopathic hemolytic anemia and thus display schistocytes on PBS, an increased LDH level, and a decreased haptoglobin level.[35] However, coagulation studies are usually normal in TTP/HUS, whereas clotting times are prolonged in disseminated intravascular coagulation. Regardless, suspected TTP/HUS requires a hematology consultation.

The third step is consideration of both drug-related thrombocytopenia and hypersplenism in all instances.[36-38] Thrombocytopenia is more likely to occur in the presence of hypersplenism associated with cirrhosis.[39] The most frequently implicated drugs in thrombocytopenia are antibiot-

ics including trimethoprim-sulfamethoxazole, cardiac medications (eg, quinidine, procainamide), thiazide diuretics, antirheumatics including gold salts, and heparin.[36] Heparin-induced thrombocytopenia is potentially catastrophic and requires immediate cessation of drug use, including heparin flushes.[40] A diagnosis of heparin-induced thrombocytopenia may be confirmed by in vitro testing to detect heparin-dependent platelet antibodies.

After microangiopathic hemolytic anemia, drug-induced thrombocytopenia, and hypersplenism have been ruled out, idiopathic thrombocytopenic purpura (ITP) becomes the major contender in the differential diagnosis of isolated thrombocytopenia.[41-43] However, ITP is currently a diagnosis of exclusion that requires consideration of other causes of immune-mediated thrombocytopenia including connective tissue disease, lymphoproliferative disorders, and human immunodeficiency virus (HIV) infection.[44] Therefore, we recommend laboratory tests for HIV, antinuclear antibodies, and monoclonal protein for further investigation. In contrast, neither platelet antibody test nor
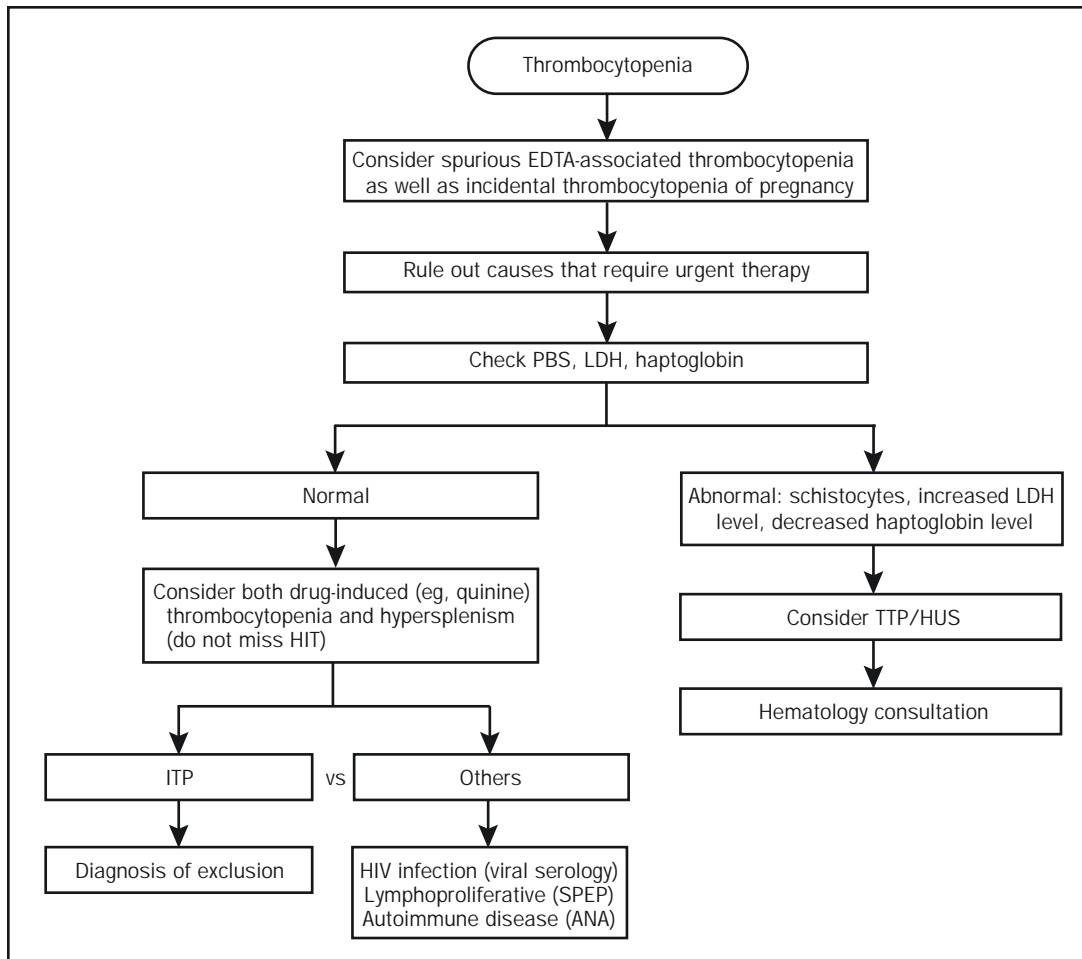
FIGURE 4. Diagnostic approach to thrombocytopenia. ANA = antinuclear antibody; DIC = disseminated intravascular coagulation; HIT = heparin-induced thrombocytopenia; HIV = human immunodeficiency virus; ITP = idiopathic thrombocytopenic purpura; LDH = lactate dehydrogenase; PBS = peripheral blood smear; SPEP = serum protein electrophoresis; TTP/HUS = thrombotic thrombocytopenic purpura/hemolytic uremic syndrome.

bone marrow biopsy is indicated in the work-up of most patients with isolated thrombocytopenia that is consistent with ITP.[45]

Rare causes of isolated thrombocytopenia include hereditary thrombocytopenias that may be associated with giant platelets on PBS (eg, May-Hegglin anomaly, gray platelet syndrome, Bernard-Soulier syndrome, and X-linked Wiskott-Aldrich syndrome),[46] myelodysplastic syndrome (MDS) (rarely presents with isolated thrombocytopenia),[47] amegakaryocytic thrombocytopenia (a bone marrow biopsy is required for diagnosis),[48] and posttransfusion purpura (a rare complication of blood transfusion).[49] A history of blood component transfusion at 1 to 2 weeks before onset of thrombocytopenia should suggest posttransfusion purpura. In all the aforementioned situations, a hematology consultation is advised.

LEUKOPENIA

NEUTROPENIA

The absolute neutrophil count (ANC) is either derived by multiplying the total leukocyte count by the percentage of band neutrophils and segmented neutrophils or obtained directly from an electronic cell counter. Neutropenia is clinically most relevant when it is severe (ANC, $<0.5 \times 10^9$/L) because of the associated risk of infection.[50] Severe neutropenia is classified into congenital and acquired categories. The congenital category includes Kostmann syndrome (congenital agranulocytosis), cyclic neutropenia, and other lesser known entities.[51] Both hematology and medical genetics consultations are advised for patients with congenital severe neutropenia but not for those with benign chronic neutropenia that occurs usually in persons of Afri-

TABLE 3. **Drugs Frequently Implicated in Neutropenia**

Drug category	Drugs
Anticonvulsants	Carbamazepine, valproic acid, diphenylhydantoin
Thyroid inhibitors	Carbimazole, methimazole, propylthiouracil
Antibiotics	Penicillins, cephalosporins, sulfonamides, chloramphenicol, vancomycin, trimethoprim-sulfamethoxazole
Antipsychotics	Clozapine
Antiarrhythmics	Procainamide
Antirheumatics	Gold salts, hydroxychloroquine, penicillamine
Aminosalicylates	
Nonsteroidal anti-inflammatory drugs	

can or Yemenite Jewish ancestry without sparing other ethnic groups.[52-56] The ANC in benign chronic neutropenia ranges usually between 0.5×10^9/L and 1.5×10^9/L, and the clinical course is asymptomatic.

The most frequent cause of acquired neutropenia is drug therapy; the most commonly implicated agents are listed in Table 3.[51,57,58] However, any drug should be assumed to be a potential offender until proved otherwise. Infection is another common cause of neutropenia, and the major culprits are viruses and sepsis. In the clinical setting, where either drug- or infection-associated neutropenia is suspected, appropriate immediate measures include discontinuation of the presumed offending agent, close monitoring of daily CBC, and consideration of treatment with a myeloid growth factor in patients with uncontrolled bacterial or fungal infection.

Other causes of acquired neutropenia include immune neutropenia, large granular lymphocyte (LGL) leukemia, and other hematologic malignancies that present only rarely with isolated neutropenia (eg, MDS).[51,59-61] In all such patients, we recommend PBS, lymphocyte immunophenotyping by flow cytometry, T-cell receptor (TCR) gene rearrangement studies, and antineutrophil antibody testing as initial screening. The inability to appreciate LGLs on PBS does not rule out the possibility of LGL leukemia, and definitive diagnosis requires review of both the TCR gene rearrangement and flow cytometry results. Immune neutropenia may or may not be associated with an autoimmune disease (eg, lupus, Felty syndrome), and detection of an antineutrophil antibody supports the diagnosis.[51]

LYMPHOPENIA

The possibility of recent therapy with immunosuppressive drugs, including corticosteroids and antilymphocyte monoclonal antibodies, must be considered first in treating the patient with lymphopenia.[62,63] Other causes of acquired lymphopenia, which should be familiar to the primary care physician, include viral infections such as acquired immunodeficiency syndrome and severe acute respiratory syn-

drome,[64,65] critical illness including sepsis,[66] autoimmune and connective tissue diseases including lupus and rheumatoid arthritis,[67-69] sarcoidosis,[70] chronic renal failure,[71,72] excess alcohol use,[73] older age,[74] thymoma,[75] and tuberculosis and other bacterial infections.[76] An immunology consultation is advised if congenital lymphopenia is suspected including Bruton X-linked agammaglobulinemia (B-cell deficiency), severe combined immunodeficiency (B-cell and T-cell deficiency), and DiGeorge syndrome (T-cell deficiency).[77,78] Regarding common variable immunodeficiency, the most common primary immunodeficiency syndrome that is symptomatic, it is important to know that the lymphocyte count may or may not be normal.[79]

POLYCYTHEMIA

An "increased" Hgb always raises the possibility of polycythemia vera (PV).[80] However, many other conditions are associated with increased Hgb that indicate either a real increase in RBC mass (RCM) (true polycythemia) or a spurious perception of an increase in RCM (apparent polycythemia). True polycythemia is caused by either PV, which is a clonal myeloproliferative disorder, or a nonclonal increase in RCM that is often, but not always, driven by erythropoietin (secondary polycythemia). Therefore, PV must be distinguished from both apparent and secondary polycythemia. Figure 5 shows a way to accomplish this distinction without measuring RCM.[80] In general, we believe that a well-informed hematologist in partner with an experienced clinical pathologist should be able to make a working diagnosis of PV, based on patient history, physical examination, serum erythropoietin level, and bone marrow examination, without resorting to specialized tests.[80-82] However, a new molecular marker (a Janus kinase 2 [JAK2] tyrosine kinase activating mutation, JAK2^{V617F}) that is closely associated with PV has just been described, and current diagnostic algorithms may need to be modified accordingly (see accompanying article by Tefferi and Gilliland[83] in the current issue of the *Mayo Clinic Proceedings*).

THROMBOCYTOSIS

Thrombocytosis may represent either a myeloid malignancy (primary thrombocytosis [PT]) or a secondary process related to various clinical conditions including IDA, surgical asplenia, infection, chronic inflammation, hemolysis, tissue damage, and nonmyeloid malignancy (reactive thrombocytosis [RT]).[84] The distinction between PT and RT is clinically relevant because the former but not the latter is associated with increased risk of thrombohemorrhagic complications.[85] Patient history and physical findings are most helpful in making this distinction and are
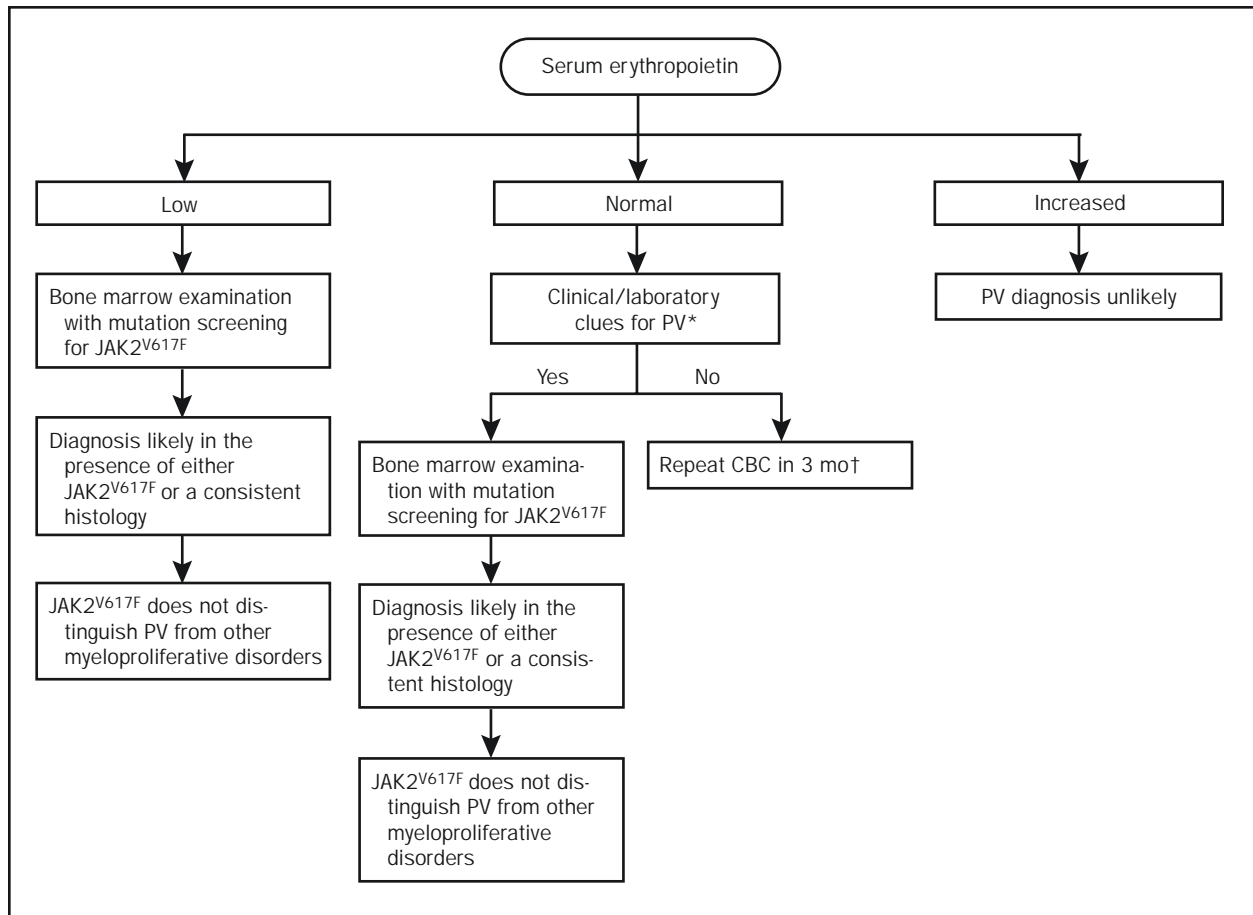
FIGURE 5. Diagnostic algorithm for polycythemia vera (PV).
*Clinical clues for PV include splenomegaly, thrombosis, aquagenic pruritus, and erythromelalgia. Laboratory clues for PV include thrombocytosis, leukocytosis, and increased leukocyte alkaline phosphatase score. Janus kinase 2 (JAK2) screening is to detect the V617F mutation that occurs in most patients with PV. BM = bone marrow; CBC = complete blood cell count; MPD = myeloproliferative disorders.
†Alternatively, one can consider mutation screening for JAK2[V617F] to help decide necessity of BM examination.

complemented by other findings on CBC: increased Hgb level, MCV, or WBC count favors a diagnosis of PT, whereas microcytic anemia suggests RT associated with IDA. In general, the degree of thrombocytosis is a poor discriminator of PT and RT, and the latter may be a possibility even when the platelet count is greater than $1000 \times 10^9/L$.[84,86]

The first step in treating a patient with thrombocytosis should be a review of old medical records to determine the duration of disease. Chronic thrombocytosis, in the absence of surgical asplenia, is highly suggestive of PT. Initial laboratory tests in this instance, as well as in the absence of clinical evidence for RT, should include PBS, serum ferritin, and C-reactive protein[87] (Figure 6). Platelet morphology is normal in RT, but the PBS may reveal the presence of Howell-Jolly bodies in patients with asplenia,

anisocytosis and poikilocytosis in patients with IDA, and polychromasia in patients with hemolysis. A normal serum ferritin level excludes the possibility of IDA-associated RT. However, a low serum ferritin level does not exclude the possibility of PT. A measurement of C-reactive protein is helpful in examining the possibility of an occult inflammatory or malignant process as a cause of RT.[87]

If the previously discussed work-up does not support a diagnosis of RT, then a bone marrow examination with cytogenetic studies as well as fluorescence in situ hybridization (FISH) for *bcr/abl* is indicated, and a hematology consultation is required to accurately interpret the test results.[88] One must remember that essential thrombocythemia (ET) is not the only cause of PT; other causes include chronic myeloid leukemia (CML), MDS, and the cellular phase of myelofibrosis with myeloid metaplasia.
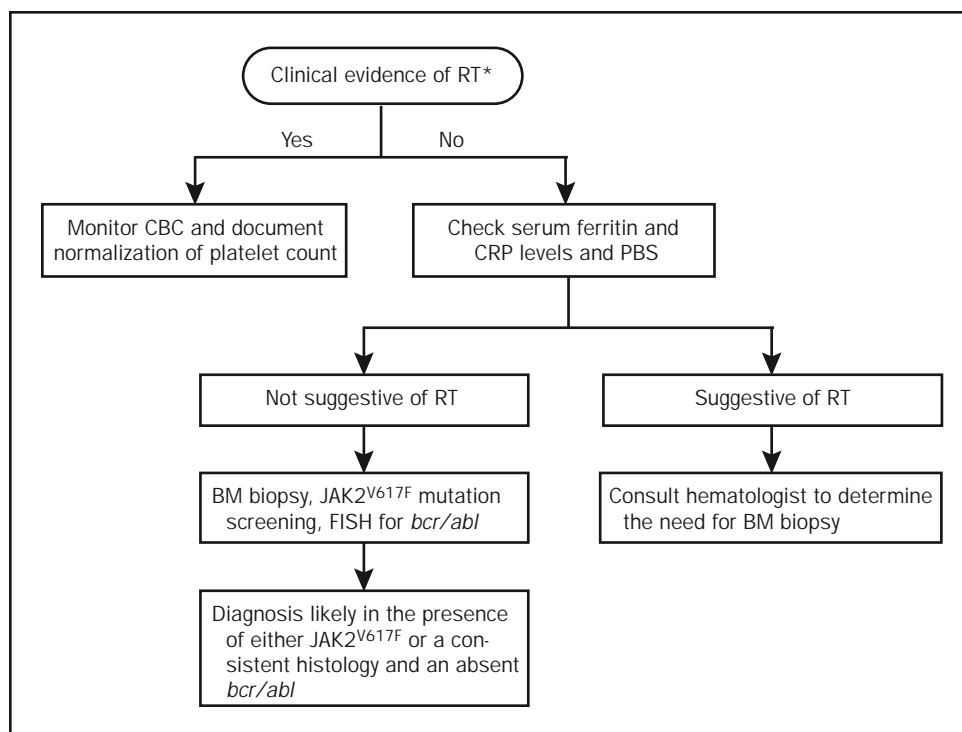
FIGURE 6. Diagnostic approach to thrombocytosis.
*Clinical evidence of reactive thrombocytosis (RT) includes the presence of infection, inflammatory condition, trauma or surgery, malignancy, hemolytic anemia, iron deficiency anemia, recent bleeding, and history of splenectomy. BM = bone marrow; CBC = complete blood cell count; CRP = C-reactive protein; FISH = fluorescence in situ hybridization; JAK2 = Janus kinase 2; PBS = peripheral blood smear. See text for interpretation of results of testing for serum ferritin and CRP levels and PBS.

Therefore, before a working diagnosis of ET is made, at a minimum the absence of the *bcr/abl* mutation must be determined by FISH.[89] As mentioned previously for PV, the presence of the newly described JAK2 mutation (JAK2^{V617F}) favors ET as opposed to RT but cannot distinguish ET from PV (see accompanying article by Tefferi and Gilliland[83] in the current issue of the *Mayo Clinic Proceedings*).

LEUKOCYTOSIS

The first step in evaluating an increased WBC count (leukocytosis) is to examine the WBC differential to determine which WBC type is in excess. The differential usually is reported along with the WBC count at no extra charge. The increase in WBCs may be secondary to either immature precursors or blasts (acute leukemia) or expansion of the aforementioned mature leukocyte types (granulocytes, lymphocytes, monocytes). Therefore, a PBS is recommended to exclude the possibility of acute leukemia and to classify the process as granulocytosis, monocytosis, or lymphocytosis. Each of these can be reactive or neoplastic (clonal).

GRANULOCYTOSIS

Neutrophilia. Neutrophilia represents either a reactive phenomenon (leukemoid reaction) or a myeloid malignancy.[90] A leukemoid reaction often is associated with infection, inflammation, malignancy, or use of drugs including glucocorticoids, psychiatric medications, and myeloid growth factors.[91-99] Therefore, patient history and findings on physical examination dictate whether further laboratory investigation is necessary to determine the cause of the increased WBC count. Further evaluation, if indicated, starts with a PBS that may show circulating blasts (suggesting acute leukemia), leukoerythroblastic results (suggesting myelofibrosis with myeloid metaplasia or other marrow-infiltrating process), or simply left-shifted neutrophilia. Left-shifted neutrophilia suggests either CML or another myeloproliferative disorder[100]; a leukemoid reaction must be distinguished from both of these conditions, and neither the degree of left-shifted granulocytosis nor the leukocyte alkaline phosphatase score is considered diagnostically adequate.[101] Therefore, if the patient's history does not suggest a leukemoid reaction, we recommend peripheral blood FISH for *bcr/abl* to rule out

TABLE 4. **Variants of Chronic Lymphoid Leukemia and Their Immunophenotypic Profile**

Type	Immunophenotypic profile
B-cell chronic lymphocytic leukemia (CLL)	CD20+(dim)sIg(dim)CD5+CD23+
Hairy cell leukemia (B cell)	CD20+(bright),sIg(bright),CD11c+(bright)CD5−CD25+(bright)CD103+
Hairy cell leukemia-variant (B cell)	CD20+(bright),sIg(bright),CD11c+(bright)CD5−CD25−CD103−
Mantle cell lymphoma (B cell)	CD20+(bright)sIg(bright),CD5+CD23−CD22+FMC7+
Small cleaved cell leukemia (B cell)	CD20+(bright)sIg(bright)CD5−CD10+
Splenic marginal zone lymphoma (B cell)	CD20+(bright),CD22+,sIg(bright),CD5−,CD10−,CD25−,CD103−,CD11c+/−
Lymphoplasmacytoid lymphoma (Waldenström)	CD20+,CD22+,sIg(bright),CD5−,CD10−,CD25−,CD103−,CD11c+/−
B-prolymphocytic leukemia	CD20+(bright),sIg(bright),CD5−CD23−FMC7+
T-prolymphocytic leukemia (T-helper CLL)	CD3+CD7+CD4+CD5+CD8+/−CD25−
Hepatosplenic γ/δ T-cell lymphoma	CD2+(bright)CD3+CD7+CD16+CD4−CD8−/+CD5−CD25−, γ/δ receptor+
T-large granular lymphocyte leukemia	CD3+CD8+(dim)CD2+(dim)CD4−CD57+CD16+
Adult T-cell leukemia/lymphoma (ATL)	CD3+(dim)CD7−CD4+CD25+
Sézary syndrome (T cell)	CD3+(dim)CD7−CD4+CD8−CD25−
Chronic natural killer cell lymphocytosis	CD3−CD20−CD16+CD56+

the possibility of CML in mild cases of mature neutrophilia (WBC, <20 × 10⁹/L).[89] A hematology consultation is required in the presence of either a higher degree of leukocytosis or left-shift. Also of note, a rare form of myeloid malignancy, chronic neutrophilic leukemia, presents with mature neutrophilia and minimal left-shift.[102]

Eosinophilia. The first step in treating a patient with blood eosinophilia is to exclude the possibility of "secondary" eosinophilia caused by parasite infestation, drugs, comorbid conditions such as asthma and other allergic conditions, vasculitides, lymphoma, and metastatic cancer.[103] Therefore, the initial approach should include obtaining a good patient history and ordering a stool test for ova and parasites. In contrast, in all patients with "primary" eosinophilia, a bone marrow biopsy is recommended to distinguish between clonal eosinophilia and the hypereosinophilic syndrome (HES).[103] Bone marrow examination in patients with suspected HES should include cytogenetic studies, FISH for *FIP1L1-PDGFRA* mutation, immunohistochemical stains for tryptase, and mast cell immunophenotyping. These tests are necessary to determine whether a patient will respond to treatment with imatinib mesylate.[104,105]

Additional blood studies that are currently considered during the evaluation of primary eosinophilia include serum tryptase (an increased level suggests mastocytosis and warrants molecular studies to detect *FIP1L1-PDGFRA*), T-cell immunophenotyping as well as TCR gene rearrangement analysis (positive test results suggest an underlying clonal T-cell disorder), serum interleukin 5 (an elevated level requires careful evaluation of the bone marrow for the presence of a clonal T-cell disease), and serum IgE level (patients with increased IgE level may be at a lower risk of developing eosinphilia-associated heart disease).[103] In addition to looking for the cause of eosinophilia, initial evaluation also should include laboratory tests to assess possible

eosinophilic-mediated tissue damage. Noninvasive tests include chest radiography, pulmonary function tests, echocardiography, and measurement of serum troponin levels. An increased level of serum cardiac troponin has been shown to correlate with the presence of cardiomyopathy in HES.[103]

Basophilia. Peripheral blood basophilia is an extremely rare condition that suggests chronic basophilic leukemia.[106] Such a finding requires a bone marrow examination and a prompt hematology consultation.

MONOCYTOSIS

Absolute monocytosis that is persistent should be considered a marker of a myeloproliferative disorder (eg, chronic myelomonocytic leukemia) until proved otherwise by bone marrow examination and cytogenetic studies.[107] Therefore, we recommend a hematology consultation for further evaluation. Relative monocytosis often is seen during recovery from chemotherapy or drug-induced neutropenia and does not require additional work-up. Reactive absolute monocytosis rarely may accompany chronic infectious, inflammatory, or granulomatous processes as well as metastatic cancer, lymphoma, radiation therapy, and depression and may follow acute myocardial infection.[108-112]

LYMPHOCYTOSIS

The first step in the evaluation of lymphocytosis is a PBS to review the morphology of the excess lymphocytes. Reactive lymphocytosis is characterized by LGL morphology and must be distinguished from LGL leukemia.[59,60,113] Reactive T-cell lymphocytosis (eg, from viral infection) and LGL leukemia can be distinguished by the nonhematologist by TCR gene rearrangement studies from the peripheral blood. However, a specific test should not be ordered if the clinical scenario is consistent with viral infection; after the patient recovers, the CBC and PBS should

be repeated to see whether the abnormality has resolved. Similarly, a mild increase in LGL level with no symptoms or cytopenia may require no further investigation.

Lymphocytosis with normal-appearing small-lymphocyte morphology suggests B-cell chronic lymphocytic leukemia.[114] A spectrum of other morphologic abnormalities characterize other lymphoid neoplasms including acute leukemia (leukemic blasts could be mistaken for lymphocytes) or chronic lymphoid leukemias that are not chronic lymphocytic leukemia (Table 4). Such processes may be derived from B-cell, T-cell, or natural killer cell lineage.[114] However, the PBS has limited value in the differential diagnosis of lymphocytosis; we recommend, in addition, immunophenotyping by flow cytometry in all such cases. The immunophenotypic profile that accompanies the myriad of chronic lymphoid leukemia is outlined in Table 4 as a resource for the hematologist. In general, we recommend a hematology consultation for any lymphocytosis that is not reactive.

CONCLUSION

A nonhematologist should be able to address some but not all CBC abnormalities. We hope to have provided some guidance in this regard. In general, it is prudent to perform a PBS in most instances of abnormal CBC, along with basic tests that are dictated by the type of CBC abnormalities. The latter may include, for example, serum ferritin in patients with microcytic anemia or lymphocyte immunophenotyping by flow cytometry in patients with lymphocytosis; whether a hematology consultation is needed can be based on the initial laboratory results, which always are reviewed in the context of the clinical history. However, a prompt hematology consultation is encouraged in patients with severe cytopenia, pancytopenia, or extreme cytosis of any type or when a PBS report suggests TTP or acute leukemia. Finally, we strongly encourage the practice of always reviewing old medical records before initiating a costly work-up of an "abnormal" CBC.

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Questions About Abnormal CBC in Adults

1. A 68-year-old woman was found to have an increased WBC count on routine laboratory testing. The PBS revealed lymphocytosis with mature-appearing morphology. Immunophenotyping by flow cytometry revealed a monoclonal (ie, light chain–restricted) B-cell population that expressed CD20 (bright), CD5, but not CD23 or CD10. Which *one* of the following is the *most likely* diagnosis?

   a. Hairy cell leukemia
   b. Mantle cell lymphoma
   c. B-cell chronic lymphocytic leukemia
   d. Small cleaved cell leukemia
   e. Marginal zone lymphoma

2. During evaluation for microcytic anemia in a patient with rheumatoid arthritis, the patient's serum ferritin level was found to have increased. Which *one* of the following statements is *true* regarding this case?

   a. IDA is unlikely
   b. IDA cannot be ruled out
   c. The patient could have both IDA and ACD
   d. ACD is unlikely
   e. Thalassemia can be ruled out

3. During evaluation for low normal serum B_{12} level associated with normocytic anemia, the patient's serum homocysteine level was found to be normal. Which *one* of the following statements is *false* regarding this case?

   a. PA is unlikely
   b. The serum methylmalonic acid level must be determined to rule out B_{12} deficiency
   c. The Schilling test is not necessary
   d. The PBS is unlikely to show hypersegmented neutrophils
   e. B_{12} deficiency is not always associated with macrocytic anemia

4. A 20-year-old African American man presents with a WBC count of 3×10^9/L. The WBC differential reveals an ANC of 1.2×10^9/L. The patient is completely asymptomatic, and his family history, medical history, and medication history are all unremarkable. Review of old medical records shows that the patient usually has a mildly low WBC count. Which *one* of the following is the *next appropriate* step?

   a. Bone marrow biopsy
   b. Hematology consultation
   c. Periodic monitoring of WBC count with no further investigation at this point
   d. Long-term use of myeloid growth factors to keep the WBC count normal
   e. Long-term use of prophylactic antibiotics

5. A 33-year-old white man presents with heart failure and blood eosinophilia (absolute eosinophil count, 5 $\times 10^9$/L). Extensive work-up disclosed no cause for reactive eosinophilia. Which *one* of the following tests provides the *most treatment-relevant* information?

   a. Serum interleukin 5 level
   b. PBS or bone marrow FISH for *CHIC2* deletion
   c. T-cell immunophenotyping and TCR gene rearrangement studies
   d. Bone marrow histological examination
   e. Bone marrow karyotype analysis

Correct answers:
1. *b*, 2. *a*, 3. *b*, 4. *c*, 5. *b*