Decoding the CBC

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Disclosures

None

Objectives

- What are different types of blood cells
- How do cells differentiate
- Why is it important to know what each cell line does
- Common conditions diagnosed with CBC
- When to refer

Hematology

- Prior to consulting Hematology
  - What do you want to know
    - Be clear
    - Be specific
  - Why
    - Helps to limit health care costs
    - Answers the question you want asked

Hematology

- What do we do?
- Malignant hematologic conditions
  - Multiple Myeloma
  - Acute Leukemias
  - Chronic leukemias
  - Myeloproliferative Disorders

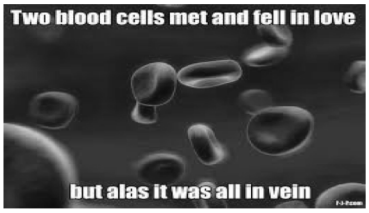
Hematology

- What we do?
- Non-Malignant conditions
  - Anemias
  - Thrombocytopenia
  - Secondary polycythemia
  - Clotting disorders

Hematology

- Website:
  - Hematology.org
    - Click on education
    - Click on Resources for clinicians
    - Right hand side: Quick links:
      - Blood: How I treat

So…About that CBC

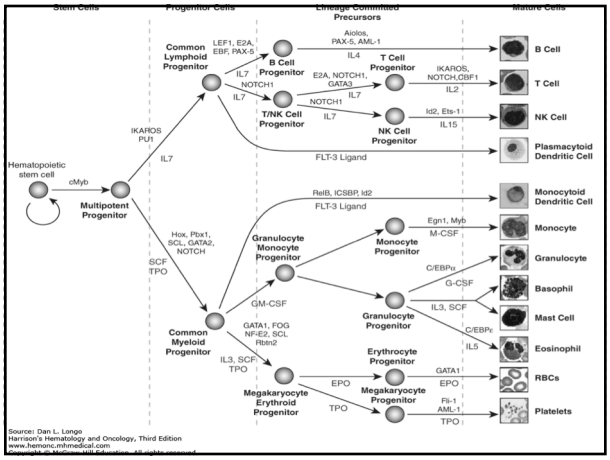


Hematopoietic stem cells

- Hemo-blood
- Poiesis-creation
- What do stem cells do?
  - Self-renewal
  - differentiation

Stem cell function

- Stem cells are multipotent
  - Long term (years)
  - Short term (months)
- 3 main functions
  - Generate new cells
  - Maintain function
  - Repair



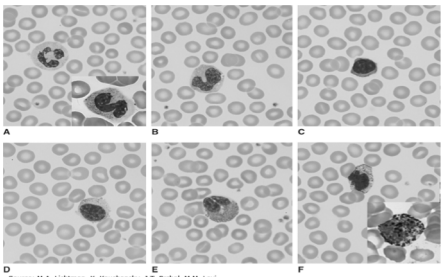
Hematopoietic stem cells

- Self-renewal
  - Balancing act of 3 mechanisms
    - Apoptosis
      - Cell death
    - Self-renewal
      - Critical for regulating the number of stem cells
    - Differentiation
      - Uncontrolled leads to hematologic malignant conditions

White Blood Cells

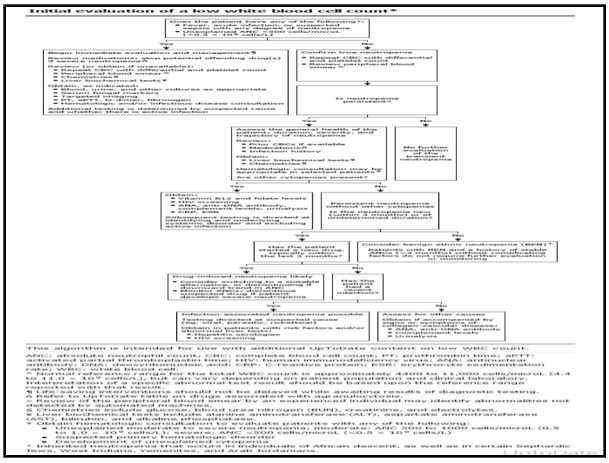
- Myeloid cell line
  - Neutrophils
  - Eosinophils
  - Basophils
  - Monocytes
- Lymphoid cell line
  - lymphocytes
    - T-cells
    - B-cells

Neutrophils



Neutrophils

- Normal Neutrophils
  - Approximately between $1.5X10^9/L$-$6.5X10^9/L$
  - At birth- normal is approximately 12 $X10^9/L$
- Neutropenia
  - <0.5 $X10^9/L$ [500/uL]
- Neutrophilia
  - >7.5 $X10^9/L$ (adults)



Neutropenia

- Inherited or acquired
  - Severe aplastic anemia, Fanconi's anemia
  - Congenital neutropenia
  - Benign ethnic neutropenia (BEN)
- Nutritional Deficiency
  - B12 Deficiency
  - Folate deficiency
  - Copper
  - Alcoholism

Neutropenia

- Medications
  - Cytotoxic drugs
  - Immunosuppressive medications
- Infection
  - Epstein-Barr virus
  - HIV
  - Hepatitis
  - Parasites
  - Bacterial infections

Major medications with a definite association with agranulocytosis

Antithyroid drugs (thionamides)	**Antibiotics**
Methimazole	Macrolides
Carbimazole	Trimethoprim-sulfamethoxazole
Propylthiouracil	Chloramphenicol
Antiinflammatory drugs	Sulfonamides
Sulfasalazine	Semisynthetic penicillins
Nonsteroidal antiinflammatory drugs	Vancomycin
Gold salts	Cephalosporins
Penicillamine	Dapsone
Phenylbutazone	**Antimalarial drugs**
Antipyrine	Amodiaquine
Dipyrone	Chloroquine
Phenacetin	Quinine
Psychotropic drugs	**Antifungal agents**
Clozapine	Amphotericin B
Phenothiazines	Flucytosine
Tricyclic and tetracyclic antidepressants	**Anticonvulsants**
Meprobamate	Carbamazepine
Cocaine/heroin (adulterated with levamisole)	Phenytoin
Gastrointestinal drugs	Ethosuximide
Sulfasalazine	Valproate
Histamine H2- receptor antagonists	**Diuretics**
Cardiovascular drugs	Thiazides
Antiarrhythmic agents (tocainide, procainamide, flecainide)	Acetazolamide
Ticlopidine	Furosemide
ACE inhibitors (enalapril, captopril)	Spironolactone
Propranolol	**Sulfonylureas**
Dipyridamole	Chlorpropamide
Digoxin	Tolbutamide
Dermatologic drugs	**Iron chelating agents**
Dapsone	Deferiprone
Isotretinoin	

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Neutrophilia

- Neutrophils
  - Diurnal-peak late in the day
  - Peak in the afternoon
- Acute neutrophilia
  - Inflammation-stress, exercise
  - Infection
  - Surgery, GI hemorrhage
  - Thermal burns, electric shock
  - Systemic vasculitis
  - Myocardial infarction-more severe with neutrophilia
  - Pulmonary Embolism
  - Sickle cell anemia

Neutrophilia

- Chronic neutrophilia
  - Endotoxins
  - Glucocorticoids
  - Polycythemia Vera, Chronic Myelogenous Leukemia
  - Cigarette smokers
  - Rheumatoid arthritis
  - Osteomyelitis
  - Ulcerative colitis
  - Gout
  - Sweet Syndrome
  - Lung and gastrointestinal cancer-especially metastasis

Classification of neutrophilia

Spurious
Platelet clumping
Mixed cryoglobulinemia
Primary (no other evident associated disease)
Myeloproliferative disorders (eg, CML, PV, ET)
Hereditary neutrophilia
Chronic idiopathic neutrophilia
Familial myeloproliferative disease
Congenital anomalies and leukemoid reaction
Down syndrome
Leukocyte adhesion factor deficiency
Familial cold urticaria and leukocytosis
Secondary
Infection
Stress (physical or emotional stress, vigorous exercise)
Cigarette smoking
Drugs
Glucocorticoids
Recombinant G-CSF or GM-CSF*
Catecholamines (epinephrine)
Lithium
All-trans retinoic acid
Isolated case reports for occasional other drugs
Nonhematologic malignancy
Heatstroke
Generalized bone marrow stimulation (as in hemolysis)
Asplenia and hyposplenism

Most commonly encountered causes of neutrophilia are shown in **bold**.

CML: chronic myelogenous leukemia; PV: polycythemia vera; ET: essential thrombocythemia; G-CSF: granulocyte colony-stimulating factor; GM-CSF: granulocyte-macrophage colony-stimulating factor.
* These agents are used therapeutically to raise the neutrophil count.

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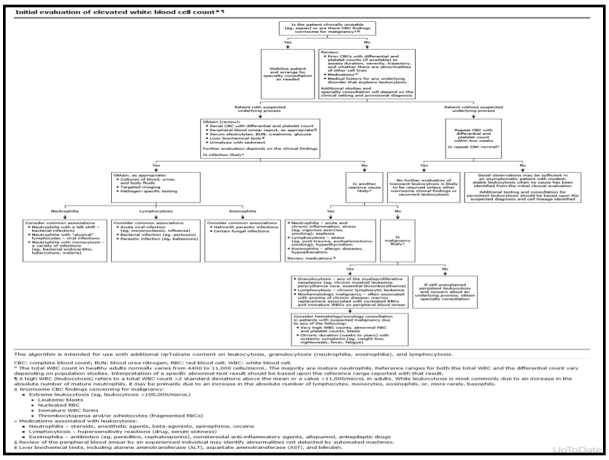
Initial evaluation of elevated white blood cell count* ¶



This algorithm is intended for use with additional UpToDate content on leukocytosis, granulocytosis (neutrophilia, eosinophilia), and lymphocytosis.

CBC: complete blood count; BUN: blood urea nitrogen; RBC: red blood cell; WBC: white blood cell.
* The total WBC count in healthy adults normally varies from 4400 to 11,000 cells/microL. The majority are mature neutrophils. Reference ranges for both the total WBC and the differential count vary depending on population studies. Interpretation of a specific abnormal test result should be based upon the reference range reported with that result.
¶ A high WBC count (leukocytosis) refers to a total WBC count >2 standard deviations above the mean or a value >11,000/microL in adults. White leukocytosis is most commonly due to an increase in the absolute number of neutrophils, but it may also primarily due to an increase in the absolute number of lymphocytes, monocytes, eosinophils, or, more rarely, basophils.
Δ Worrisome CBC findings concerning for malignancy:
- Extreme leukocytosis (eg, leukocytosis >100,000/microL)
- Leukemic blasts
- Left shift
- Immature WBC forms
- Thrombocytopenia and/or schistocytes (fragmented RBCs)

◊ Medications associated with leukocytosis:
- Neutrophilia – steroids, anesthetic agents, beta-agonists, epinephrine, cocaine
- Eosinophilia – antibiotics (eg, penicillins, cephalosporins), nonsteroidal anti-inflammatory agents, allopurinol, antiepileptic drugs

§ Review of the peripheral blood smear by an experienced individual may identify abnormalities not detected by automated machines.
¥ Liver biochemical tests, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin.

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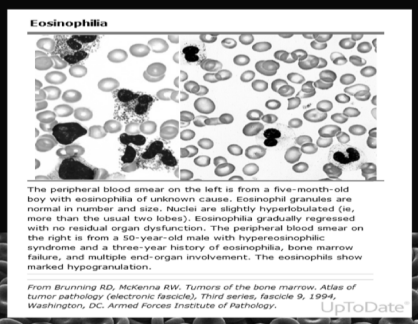
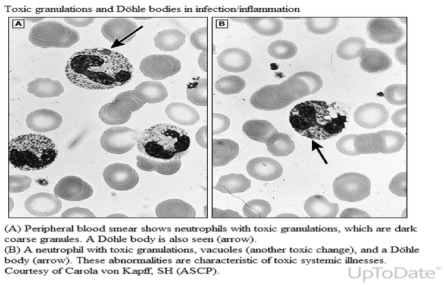
Eosinophils and/or Basophilia

- Infection
  - parasitic
- Allergies
- Cancer

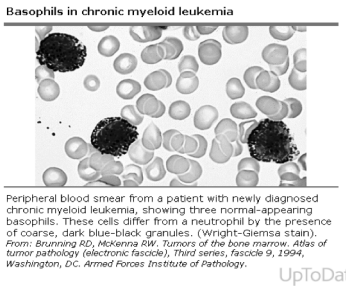
Eosinophils



Infection



Basophils



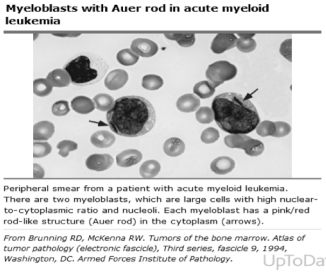
Monocytes

- Monocytes- $0.3X10^9/L$-$0.7X10^9/L$
- Phagocytes
  - Kill microorganisms
  - ingest aged or damaged blood cells
  - Antimicrobial
- Inflammatory cytokines
  - Role in sepsis
- Wound healing participant

Monocytes

- Monocytosis
  - Endocarditis
  - Tuberculosis
  - Syphilis
  - CMML-type of myelodysplastic syndrome
  - Acute myelogenous leukemia
- Monocytopenia
  - Cytotoxic chemotherapy
  - Bone marrow failure
  - Hairy cell leukemia

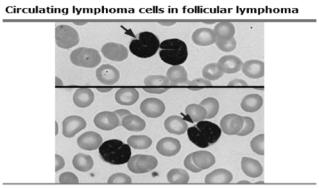
Acute Myeloid Leukemia



Lymphocytes

- Lymphocytosis->4X10^9/L
  - Chronic lymphocytic leukemia
  - Acute Lymphoblastic Leukemia
  - Lymphomas
- Secondary Lymphocytosis
  - Mononucleosis
  - EBV
  - CMV
  - Viral hepatitis
  - Dengue Fever
  - Bordetella pertussis

Lymphoma



Two fields of a peripheral blood smear from a patient with follicular lymphoma are shown here. Several cells with a "notched nucleus" (centrocytes) are seen; nuclei are partially or completely divided by a characteristic cleft (arrows). The chromatin stains intensely and is compactly clumped. These cells have also been called "buttock" cells.

From Warnke RA, Weiss LM, Chan JK, Cleary ML, Dorfman RF. Tumors of the lymph nodes and spleen. Atlas of tumor pathology (electronic fascicle), Third series, fascicle 14, 1995, Washington, DC. Armed Forces Institute of Pathology.

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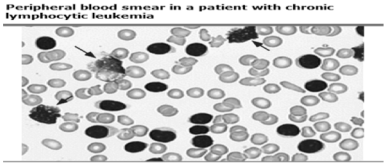
Chronic Lymphocytic Leukemia



Blood smear from a patient with B cell chronic lymphocytic leukemia. The predominant lymphocytes have a very sparse cytoplasm, round to slightly oval nuclei, and no evident nucleoli. Damaged lymphocytes ("smudge cells") are present (arrows).
From: Brunning RD, McKenna RW. Tumors of the bone marrow. Atlas of tumor pathology (electronic fascicle), Third series, fascicle 9, 1994, Washington, DC. Armed Forces Institute of Pathology.

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Lymphocytes

- Drug induced Lymphocytosis
  - Dasatanib
  - Ibrutinib

Lymphocytes

- Lymphopenias-<1.0X10^9/L
  - Immunodeficiency
  - Measles
  - West Nile encephalitis
  - Herpes virus type 6 (HHV-6)
  - Herpes virus type 8 (HHV-8)
  - Autoimmune diseases
    - Myasthenia Gravis, Systemic lupus erythematosus
  - Zinc deficiency

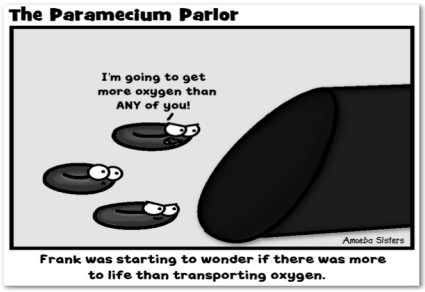
When to refer

- No referral needed
  - Mild asymptomatic neutropenia-explained by initial evaluation
  - Most common cause of mild neutropenia is Benign Ethnic Neutropenia (BEN)
- Referral- days to weeks
  - Worsening ANC-not r/t BEN, rheumatoid condition or hypersplenism
  - No improvement in nutritional interventions
  - Increased frequency of infections

When to refer

- Refer in days
  - Hairy lymphocytes
  - Smudge cells
  - Unexplained lymphadenopathy/splenomegaly
  - Increased pancytopenia
- Immediate referral-hours
  - Blasts on blood smear
  - ANC less than 200 cells/microL or $<0.2X10^9/L$

So…About that CBC



Red blood cells

- Hemoglobin
  - Oxygen carrying capacity of whole blood
  - Expressed in g/dl or g/L
- Hematocrit
  - Cell volume
  - Expressed in percent
- Red blood cell count
  - Number of RBCs contained in a specified volume of whole blood

Red blood cell indices

- MCV-mean corpuscular volume
  - Size of the patient's red blood cell
  - Low, normal or elevated
- MCH-mean corpuscular hemoglobin
  - Average amount of hemoglobin in a red blood cell
  - Low MCH may indicate
    - Hypochromia
    - thalassemia

Red blood cell indices

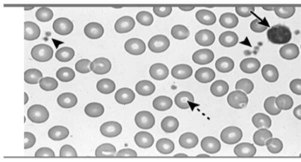
- RDW-red cell distribution width
  - Size
  - High=large variation in size
    - Iron deficiency
    - Myelodysplastic syndrome (MDS)
    - Hemoglobinopathies
    - Transfusion recipients
  - Low=homogeneity

Cycle of red blood cells

- Erythropoiesis
  - Erythropoietin-hormone is the regulator
    - Produced mostly by the kidney
    - Not stored
    - It is secreted
  - Reticulocytes tell if there is adequate erythropoiesis
    - Increased=problem

Blood smear

Normal peripheral blood smear



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

Courtesy of Carola von Kapff, SH (ASCP).

Normal values for red blood cell parameters in adults

RBC parameter	Men	Women
Hemoglobin, g/dL	15.7 (14.0 to 17.5)	13.8 (12.3 to 15.3)
Hematocrit, percent	46 (42 to 50)	40 (36 to 45)
RBC count, million/microL	5.2 (4.5 to 5.9)	4.6 (4.1 to 5.1)
Reticulocyte count, cells/microL	20,000 to 110,000	20,000 to 110,000
Reticulocyte percentage	1.6 ± 0.5	1.4 ± 0.5
Mean corpuscular volume (MCV), femtoliters (fL)	88 (80 to 96)	88 (80 to 96)
Mean cell hemoglobin (MCH), pg/RBC	30 (28 to 33)	30 (28 to 33)
Mean cell hemoglobin concentration (MCHC), g/dL of RBC	34 (33 to 36)	34 (33 to 36)
Red cell distribution width (RDW), CV, percent	13 (12 to 15)	13 (12 to 15)

Values represent the mean and reference intervals (normal range, based on nonparametric 95% confidence interval) for each sex. Reference ranges may vary slightly in different laboratories. There are no sex differences in absolute reticulocyte count, MCV, MCH, MCHC, or RDW. Values for children are presented separately in UpToDate. Refer to UpToDate topics on anemia for further details.

RBC: red blood cell; CV: coefficient of variation method.

Anemia

- 2 approaches
  - Kinetic
    - Decreased RBC production
    - Increased RBC breakdown
    - Blood loss
  - Morphologic
    - MCV
    - Reticulocyte count

Kinetic Approach

Laboratory findings during the development of iron deficiency

	Normal	Iron deficiency without anemia	Iron deficiency with mild anemia	Severe iron deficiency with severe anemia
Hemoglobin	Normal range*	Normal range*	**9 to 12 g/dL (90 to 120 g/L)**	**6 to 7 g/dL (60 to 70 g/L)**
Red blood cell size and appearance	Normal	Normal	**Normal or slight hypochromia (slight decrease in MCHC)**	**Microcytosis (decrease in MCV) and hypochromia (decrease in MCHC)**
Serum ferritin	40 to 200 ng/mL (40 to 200 mcg/L; 89.9 to 449 picoM/L)	**<40 ng/mL¶ (<40 mcg/L; <89.9 picoM/L)**	**<20 ng/mL (<20 mcg/L; <45 picoM/L)**	**<10 ng/mL (<10 mcg/L; <22.5 picoM/L)**
Serum iron	60 to 150 mcg/dL (10.7 to 26.7 microM/L)	60 to 150 mcg/dL (10.7 to 26.7 microM/L)	**<60 mcg/dL (<10.7 microM/L)**	**<40 mcg/dL (<7.1 microM/L**
Total iron-binding capacity (TIBC; transferrin)	300 to 360 mcg/dL (53.7 to 64.4 microM/L)	300 to 390 mcg/dL (53.7 to 69.8 microM/L)	**350 to 400 mcg/dL (62.6 to 71.6 microM/L)**	**>410 mcg/dL (>73.4 microM/L)**
Transferrin saturation (serum iron/TIBC)	20 to 50%	20%	**<15%**	**<10%**
Bone marrow iron stain	Adequate iron present	**Iron absent**	**Iron absent**	**Iron absent**
Erythrocyte zinc protoporphyrin, ng/mL RBC	30 to 70	30 to 70	**>100**	**100 to 200**

Bold type illustrates the progression of changes and the tests most likely to define the various stages of iron deficiency. Decreased serum ferritin and absent bone marrow iron are the earliest changes, followed by decreases in the transferrin saturation. Serum iron may be low in anemia of chronic disease or increased by a recent meal or normal diurnal variation and by itself cannot be used to diagnose iron deficiency. Serum ferritin may be increased by other conditions such as acute inflammation, liver disease, and idiopathic pulmonary hemosiderosis, making diagnosis of iron deficiency more challenging. Testing iron studies using a fasting sample may be helpful if there is concern that oral iron intake has affected the serum iron level, which in turn may affect the TSAT. Bone marrow iron staining (the gold standard) and erythrocyte zinc protoporphyrin (a nonspecific finding) are not routinely used in the evaluation or diagnosis of iron deficiency. Refer to UpToDate for our approach to diagnostic testing.

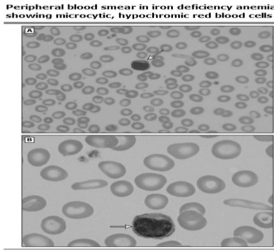
MCHC: mean corpuscular hemoglobin concentration; MCV: mean corpuscular volume; TIBC: total iron binding capacity; RBC: red blood cell; TSAT: transferrin saturation.

* The normal range for hemoglobin varies by age and sex (adult men, 14 to 17.5 g/dL; adult women, 12.3 to 15.3 g/dL; children, refer to UpToDate topic on anemia in children).

¶ The exact value is not well established; some clinicians may use a lower value for diagnosing iron deficiency.

Iron deficiency

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

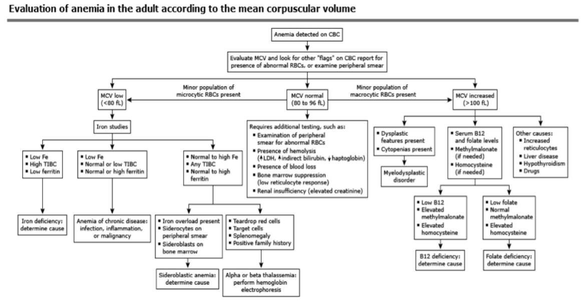


The same peripheral blood smear from a patient with iron deficiency is shown at two different magnifications. Small (microcytic) red blood cells are shown, many of which have a thin rim of pink hemoglobin (hypochromia). Occasional "pencil"-shaped cells are also present. A small lymphocyte is shown for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

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

Morphologic Approach

Evaluation of anemia in the adult according to the mean corpuscular volume



CBC: complete blood count; MCV: mean corpuscular volume; RBCs: red blood cells; Fe: iron; TIBC: total iron-binding capacity (transferrin); LDH: lactate dehydrogenase.

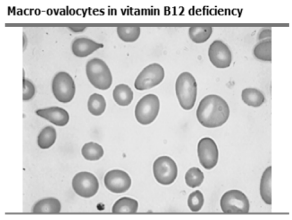
Anemia from Nutritional Deficiencies

- Vitamin A deficiency-prevalent in school children in underdeveloped African countries
  - Decreased MCV
  - Decreased RBC concentration
  - Anisocytosis and poikilocytosis- on smear
- Vitamin B6 deficiency
  - Hypochromic microcytic anemia
  - Malabsorptive states
  - Dialysis
  - medications

Anemia from Nutritional Deficiencies

- Vitamin E deficiency
  - Caused by chronic fat malabsorption (Cystic Fibrosis)
  - Sickle cell disease-increase in irreversibly sickled cells
- Copper deficiency
  - Malnourished children-
    - osteoporosis, flaring ribs, bony abnormalities
  - Gastric bypass/bariatric surgery
    - Macrocytic anemia, neutropenia, ringed sideroblasts- can mimic MDS.
  - Elevated zinc

B12 Deficiency



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

Courtesy of Stanley L Schrier, MD. UpToDate®

Anemia

Differential diagnosis of anemia in the adult

Low mean corpuscular volume (microcytic anemia: MCV <80 fL)
Iron deficiency anemia
Thalassemic disorders
Anemia of inflammation/anemia of chronic disease (late; uncommon)
Sideroblastic anemia (eg, congenital, lead, alcohol, drugs; uncommon)
Copper deficiency, zinc poisoning (rare)
Hemolysis**
Normal mean corpuscular volume (normocytic anemia: MCV 80 to 100 fL)
Acute blood loss
Iron deficiency anemia (early)
Anemia of inflammation/anemia of chronic disease (eg, infection, inflammation, malignancy)
Bone marrow suppression (may also be macrocytic)
Bone marrow invasion (eg, leukoerythroblastic blood picture)
Acquired pure red blood cell aplasia
Aplastic anemia
Chronic renal insufficiency
Endocrine dysfunction
Hypothyroidism (most commonly normocytic)
Hypopituitarism
Hemolysis**
Increased mean corpuscular volume (macrocytic anemia: MCV >100 fL)
Excessive ethanol use
Folate deficiency
Vitamin B12 deficiency
Myelodysplastic syndromes
Acute myeloid leukemias (eg, erythroleukemia)
Reticulocytosis
Response to hemolysis**
Response to blood loss
Response to appropriate hematinic (eg, iron, vitamin B12, folic acid)
Drug-induced anemia (eg, hydroxyurea, AZT, chemotherapeutic agents)
Liver disease
Hypothyroidism (less commonly macrocytic)

This list is not meant to be exhaustive; only the most common causes are mentioned. In addition, two or more of these conditions may be present (eg, combined iron and folate deficiencies), resulting in a misleadingly normal mean corpuscular volume. Refer to UpToDate for the approach to anemia as well as topics on specific disorders for more details.

MCV: mean corpuscular volume; fL: femtoliters; AZT: zidovudine.

** Hemolysis is typically associated with some degree of macrocytosis because reticulocytes, which are larger than mature red blood cells, are increased in hemolysis. However, the MCV can be low, normal, or high depending on the degree of reticulocytosis and the underlying cause of hemolysis, which determines the MCV of the remaining cells.

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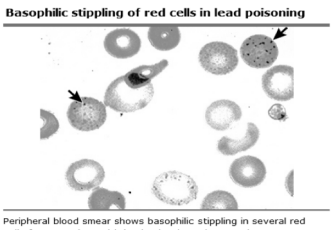
Anemia of chronic disease

- Diagnoses
  - Chronic inflammation
  - Chronic infection
- Lab values associated
  - Low serum iron
  - Low to normal transferrin
  - High to normal ferritin
- Why does this happen?
  - Inflammatory cytokines decrease erythropoiesis
  - Interleukin 6 increases hepcidin
  - Hepcidin blocks release of iron
  - =hypoferremia
  - Intervention-treat underlying disease and may be erythropoietin

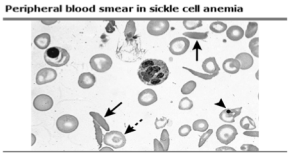
Anemia



Peripheral blood smear shows basophilic stippling in several red cells from a patient with lead poisoning. The granules represent ribosomal precipitates. A similar picture can be seen in a number of other conditions including thalassemia, megaloblastic anemia, sickle cell anemia, and sideroblastic anemia.

Courtesy of Carola von Kapff, SH (ASCP). UpToDate®

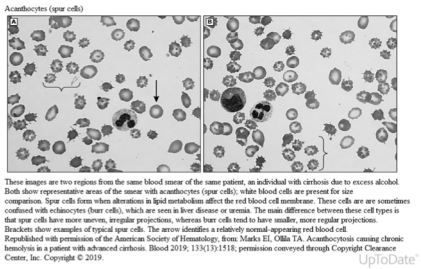
Sickle Cell Anemia



Alcoholism and Anemia

- Alcoholism can cause:
  - Nutritional deficiencies- folic acid
  - GI bleeding
  - Liver dysfunction
  - Hemolytic anemia
  - Hypersplenism
- What may be seen on the CBC
  - Mild macrocytosis
  - Iron deficiency
  - thrombocytopenia

Abnormal red blood cells



Anemia Summary

- Most diagnosed by morphologic approach
  - Microcytic
    - MCV less than 80fl
      - Iron deficiency
      - Thalassemia
      - Anemia of chronic inflammation
  - Macrocytic
    - MCV greater than 100fl
      - Alcoholism
      - Liver disease
      - Folate and B12 deficiency
      - MDS

Anemia Summary

- MCV between 80-100fl
  - Normocytic anemia
    - Get peripheral blood smear or path review
- Questions to start asking:
  - Is the patient bleeding
  - Increase red blood cell destruction?
  - Bone marrow suppression?
  - Iron deficiency?
  - Folate or B12 deficiency?

Causes and mechanisms of macrocytosis

Abnormalities of DNA metabolism
Vitamin B12 (cobalamin) deficiency
Folate deficiency
Drugs
Antiretroviral therapies for HIV infection (eg, zidovudine)
Azathioprine or 6-mercaptopurine
Capecitabine
Cladribine
Cytosine arabinoside
Hydroxyurea
Imatinib, sunitinib
Methotrexate
Shift to immature or stressed red cells
Reticulocytosis
Action of erythropoietin - skip macrocytes, stress erythrocytosis
Aplastic anemia/Fanconi anemia
Pure red cell aplasia
Primary bone marrow disorders
Myelodysplastic syndromes
Congenital dyserythropoietic anemias
Some sideroblastic anemias
Large granular lymphocyte (LGL) leukemia
Lipid abnormalities
Liver disease
Hypothyroidism
Mechanism unknown
Alcohol abuse
Multiple myeloma and other plasma cell disorders

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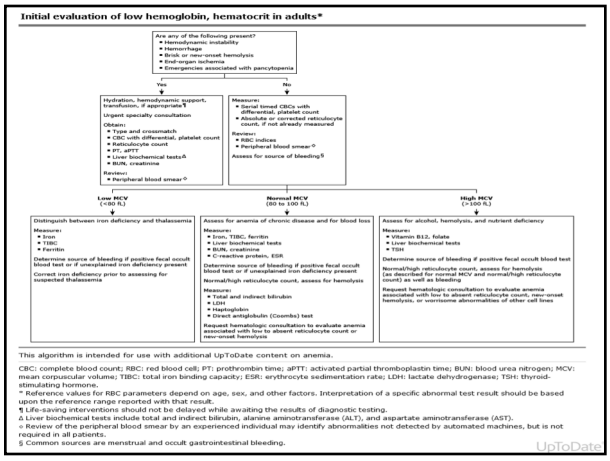
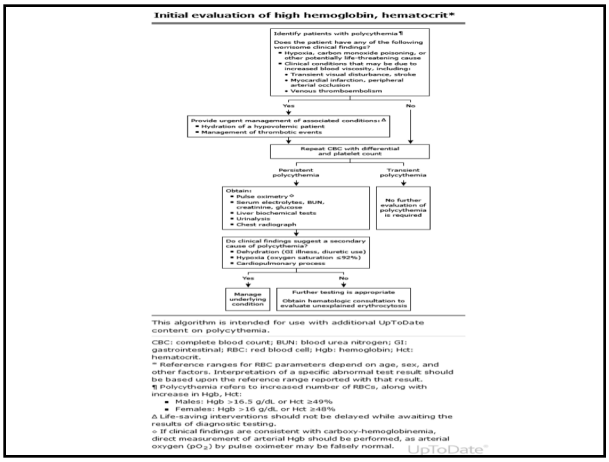


Polycythemia (erythrocytosis)

- Polycythemia is:
  - Increased hemoglobin concentration
    - Greater than 16.5g/dl for men
    - Greater than 16.0g/dl in women
  - Increased hematocrit concentration
    - Greater than 49% in men
    - Greater than 48% in women



Polycythemia

- Relative
  - Hemoconcentration
    - Diuretics, vomiting, diarrhea
    - smoking
- Absolute
  - Increase in RBC mass
    - Primary
    - Secondary

Polycythemia

- Primary
  - Mutation
    - Polycythemia vera
    - Myeloproliferative neoplasm
- Secondary
  - Physiologic response to hypoxia
    - Pulmonary disease, obstructive sleep apnea, Carbon monoxide toxicity, residence at high altitude
  - EPO secreting tumor
    - Hepatocellular carcinoma, renal cell carcinoma, pheochromocytoma, fibroid tumors

Causes of polycythemia

Relative polycythemia
Volume contraction (eg, diuretics, vomiting, diarrhea, smoking)
Absolute polycythemia
Primary polycythemia
Inherited (germline mutations)
Primary familial and congenital polycythemia (eg, *EPOR* mutation)
Chuvash polycythemia/*VHL* mutation
Congenital methemoglobinemia
High oxygen affinity hemoglobin
Bisphosphoglyceromutase (*BPGM*) mutation
Other mutations (eg, prolyl hydroxylase 2/*EGLN1*, HIF-2alpha/*EPAS1*)
Acquired (somatic mutations)
Polycythemia vera (*JAK2* mutation)
Other myeloproliferative neoplasms (eg, *JAK2*, *MPL*, *CALR* mutations)
Secondary polycythemia (elevated serum erythropoietin [EPO])
Hypoxia/cardiopulmonary-associated
Chronic pulmonary disease
Right-to-left cardiac shunts
Sleep apnea
Obesity hypoventilation syndrome (Pickwickian syndrome)
High altitude
Chronic carbon monoxide poisoning (including heavy smoking)
Kidney-associated causes
Following renal transplantation
Others (eg, renal artery stenosis, cysts, hydronephrosis)
Autonomous EPO production
EPO-producing tumors (eg, hepatocellular carcinoma, renal cell carcinoma, hemangioblastoma, pheochromocytoma, uterine leiomyomata)
Other causes
Athletic performance enhancing agents (eg, recombinant erythropoiesis stimulating agents, autologous transplantation ["blood doping"], androgens or anabolic steroids)
Cobalt toxicity
POEMS syndrome

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Evaluation of Polycythemia

- How urgent is it and what can I do before referral?
  - Medical emergencies are a no-brainer
    - Cerebral vascular accidents
    - Chest pain
  - Others related to the degree of polycythemia
    - Hematocrit of greater than 60, pruritis, abdominal fullness

      vs
    - Hematocrit of 50 and asymptomatic

Evaluation of Polycythemia

- History
  - Hyper-viscosity Symptoms
  - Thrombosis or bleeding
  - Fever/chills/night sweats/weight loss/pruritus, gout, splenomegaly
  - Dehydration
  - Cardiopulmonary disease

Evaluation of Polycythemia

- Social hx
  - Cigarette smoking
  - Exposure to carbon monoxide
  - Use of androgens
  - Use of erythropoietic agents

Evaluation of Polycythemia

- Physical exam
  - Dermatologic
  - Cardiopulmonary
  - Organomegaly

Lab testing for Polycythemia

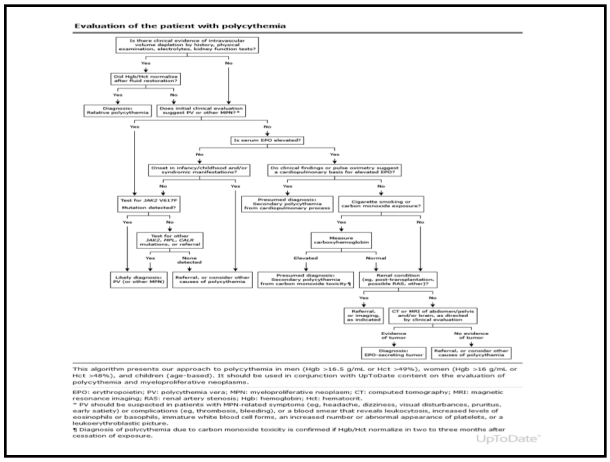
- No specific guidelines at present
  - Pulse oximetry
  - LFTs
  - Renal panel
  - Urinalysis
  - EPO level
    - Elevated=response to lack of oxygen or possible tumor
    - decreased=polycythemia vera or MPN

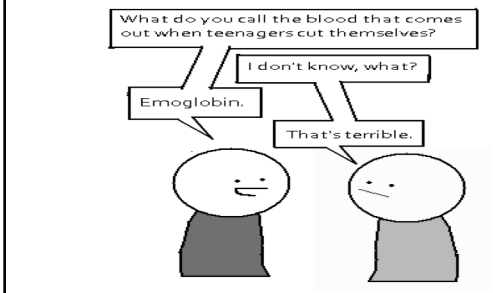
Referral

- Limit your differential prior to consultation
- Trends, Trends, Trends
  - Initial lab work to include:
    - Renal function panel
    - Liver function panel
    - Hepatitis serologies
    - Reticulocyte count
    - Iron studies to include serum, iron, TIBC, Ferritin
    - B12 and RBC folate
    - Spep/upep
    - TSH
    - Stool for occult blood

Referral

- Consult unexplained anemia with:
  - Other cytopenias
  - High LDH
  - Abnormal spep/upep
  - High reticulocyte count





Thrombocytopenia

- One of the most common referrals to hematology
- Normal platelet count 150-400 $X10^9/L$
- Platelets have a life span of 7-10 days
- One third of platelets stored in the spleen
- Two thirds in the blood vessels

Thrombocytopenia classification

- Mild
  - Above 70X $10^9/L$
- Moderate
  - 20-70 $x10^9/L$
- Severe
  - Less than 20 $X10^9/L$

Thrombocytopenia

- 5 classifications of thrombocytopenia
  1. Pseudo thrombocytopenia
     - antiphospholipid antibodies
  2. Impaired platelet production
     - ITP
     - Medications
     - Nutritional deficiencies
  3. Increased platelet destruction
     - DIC
  4. Abnormal distribution of platelets
     - Hypothermia, hypersplenism, infusions
  5. Miscellaneous causes

Causes of thrombocytopenia in adults

Falsely low platelet counts (pseudothrombocytopenia)
In vitro platelet clumping caused by ethylenediaminetetraacetic acid (EDTA)-dependent agglutinins (naturally occurring antibodies)
In vitro platelet clumping caused by an insufficiently anticoagulated specimen
In vitro platelet clumping caused by glycoprotein IIb/IIIa inhibitors (eg, abciximab) (NOTE: these can also cause true thrombocytopenia)
Giant platelets counted by automated counter as white blood cells rather than platelets
Common causes of thrombocytopenia
Primary immune thrombocytopenia (ITP)
Drug-induced immune thrombocytopenia (DITP)
Heparin (NOTE: special case, also can cause thrombosis)
Quinine (as in over-the-counter tablets for leg cramps; also in beverages)
Sulfonamides (eg, trimethoprim-sulfamethoxazole [Bactrim; Septra])
Acetaminophen (Tylenol, Panadol)
Cimetidine (Tagamet)
Ibuprofen (Advil, Motrin)
Naproxen (Aleve, Midol)
Ampicillin (Omnipen, Apo-Ampi)
Piperacillin (Pipracil, Zosyn)
Vancomycin (Vancocin)
Glycoprotein IIb/IIIa inhibitors (abciximab [ReoPro], tirofiban [Aggrastat], eptifibatide [Integrilin])
Food and beverages
Quinine-containing beverages (tonic water, Schweppes bitter lemon)
Walnuts
Certain herbal teas
Infections
HIV
Hepatitis C
Epstein-Barr virus (EBV; can be associated with infectious mononucleosis)
Helicobacter pylori (suspected in patients with symptoms of dyspepsia or peptic ulcer disease)
Sepsis with disseminated intravascular coagulation (DIC)
Intracellular parasites (eg, malaria, babesia)
Hypersplenism due to chronic liver disease
Alcohol
Nutrient deficiencies (eg, vitamin B12, folate, copper)
Rheumatologic/autoimmune disorders (eg, systemic lupus erythematosus, rheumatoid arthritis)
Pregnancy
Gestational thrombocytopenia
Preeclampsia
HELLP syndrome (hemolysis, elevated liver function tests, low platelets)
Other causes of thrombocytopenia
Myelodysplasia
Suspected in older patients, in whom a bone marrow biopsy may be appropriate
Cancer with disseminated intravascular coagulation
Cancer with bone marrow infiltration or suppression (eg, lymphoma, leukemia, some solid tumors)
Paroxysmal nocturnal hemoglobinuria (PNH)
Thrombotic microangiopathy (TMA)
Thrombotic thrombocytopenic purpura (TTP) is manifested by thrombocytopenia and microangiopathic hemolytic anemia; fever, renal failure, and/or neurologic symptoms may or may not be present
Hemolytic uremic syndrome (HUS) is typically seen in children following infection with a Shiga-toxin producing organism (*Escherichia coli* or *Shigella*)
Drug-induced TMA may occur with quinine, certain cancer therapies, calcineurin inhibitors, and others
Antiphospholipid syndrome (APS)
Aplastic anemia
Inherited thrombocytopenias
An important consideration, especially in young patients who do not respond to treatment. Some specific syndromes are listed. However, many patients appear to have autosomal dominant thrombocytopenia with no other clinical features.
Von Willebrand disease type 2B
Wiskott-Aldrich syndrome
Alport syndrome
May-Hegglin anomaly
Fanconi syndrome
Bernard-Soulier syndrome
Thrombocytopenia absent radius syndrome

The table lists possible causes of isolated thrombocytopenia. Refer to the UpToDate topics on thrombocytopenia, immune thrombocytopenia, heparin-induced thrombocytopenia, and drug-induced thrombocytopenia for further details and a more complete list of drugs that can cause drug-induced thrombocytopenia.

Common Causes of thrombocytopenia

- Alcohol is one of the leading causes in Western Countries
- Systemic Lupus Erythematosus
  - Occurs in 20-40%
- Infection
  - Bacterial
  - Viral
  - Fungal
- Chronic liver disease-d/t splenic pooling
- Medications

Drugs associated with isolated thrombocytopenia

Drug	Mechanism(s)
Abciximab	DITP
Acetaminophen	DITP; antibodies react with a drug metabolite, not the unmodified drug
Alemtuzumab	ITP-like syndrome*
Amiodarone	DITP
Beta-lactam antibiotics (eg, penicillins, cephalosporins)	DITP
Carbamazepine	DITP
Ceftriaxone	DITP
Daptomycin	Bone marrow suppression (dose-dependent)
Eptifibatide	DITP
Ethambutol	DITP
Furosemide	DITP
Gold compounds	Bone marrow suppression
Haloperidol	DITP
Heparin	Drug-dependent antibodies that also activate platelets and are associated with thrombosis
Ibuprofen	DITP; in some patients, antibodies react with the unmodified drug; in others, antibodies only react with a drug metabolite
Irinotecan	DITP
Levofloxacin	DITP
Linezolid	Bone marrow suppression (dose-dependent)
MMR vaccine	ITP-like syndrome*
Mirtazapine	DITP
Naproxen	DITP; antibodies react with a drug metabolite, not the unmodified drug
Oxaliplatin	DITP
Penicillin	DITP
Phenytoin	DITP
Piperacillin	DITP
Quinidine	DITP
Quinine¶	DITP
Ranitidine	DITP
Rifampin	DITP
Simvastatin	DITP
Sulfonamides	DITP
Suramin	DITP
Tirofiban	DITP
Trimethoprim-sulfamethoxazole	DITP; antibodies react with the sulfamethoxazole; antibodies to trimethoprim have not been identified
Valproic acid	Bone marrow suppression (dose-dependent)
VancomycinΔ	DITP

This table lists drugs with evidence for a causal association with isolated thrombocytopenia; certain foods and beverages (eg, quinine-containing beverages, certain herbal teas, walnuts) can also cause thrombocytopenia. The drugs listed in this table come from clinical data in published case reports, identification of drug-dependent, platelet-reactive antibodies, or both; it also lists their mechanisms. Criteria for evaluating reports of a drug-induced etiology include: (1) use of the drug preceded development of thrombocytopenia *and* platelet count recovery was sustained and complete following drug discontinuation; (2) no other drugs were used prior to development of thrombocytopenia *or* platelet count remained normal despite continuation or reintroduction of other drugs; (3) other etiologies for thrombocytopenia were eliminated; and (4) re-exposure to the candidate drug caused recurrent thrombocytopenia or drug-dependent antiplatelet antibodies were demonstrated. Drugs in **bold** have been most commonly implicated in a causal relationship. Drug-dependent antibodies have been shown for all agents associated with DITP. Refer to UpToDate for additional information on drug-induced thrombocytopenia.

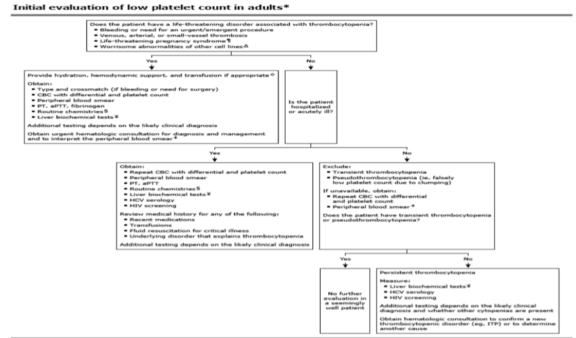
DITP: drug-induced immune thrombocytopenia (ie, thrombocytopenia caused by drug-dependent antibodies); ITP: immune thrombocytopenia, which is caused by an autoimmune mechanism that no longer requires the presence of the drug; MMR: measles, mumps, and rubella.
* A rare adverse reaction to alemtuzumab results in prolonged, severe thrombocytopenia that responds to immunosuppressive therapy.
¶ Quinine can also cause a thrombotic microangiopathy and/or other cytopenias.
Δ In addition to parenteral formulations, vancomycin may be present in orthopedic cement used for joint replacement.

Adapted from Reese JA, Li X, Hauben M, et al. Identifying drugs that cause acute thrombocytopenia: an analysis using 3 distinct methods. Blood 2010; 116:2127; George JN, Raskob GE, Shah SR, et al. Drug-induced thrombocytopenia: a systematic review of published case reports. Ann Intern Med 1998; 129:886; and Arnold DM, Nazi I, Warkentin TE, et al. Approach to the diagnosis and management of drug-induced immune thrombocytopenia. Transfusion Med Reviews, 2013; 27:137.

When to refer

- Before consultation:
  - Rule out clumping by requesting a path review if available or send test for platelet clumps specifically
  - Investigate for liver disease by:
    - Imaging
    - Substance abuse
    - Hepatitis B/C
- Consult- unexplained thrombocytopenia

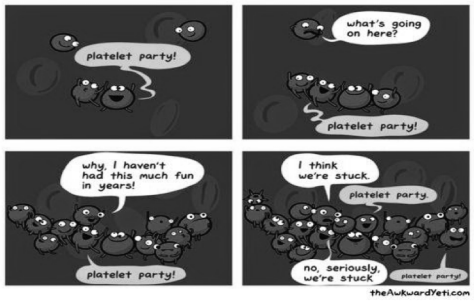
Initial evaluation of low platelet count in adults*



This algorithm is intended for use with additional UpToDate content on thrombocytopenia.

CBC: complete blood count; PT: prothrombin time; aPTT: activated thromboplastin time; HCV: hepatitis C virus; ITP: immune thrombocytopenia (idiopathic thrombocytopenic purpura); HIT: heparin-induced thrombocytopenia; HUS: hemolytic uremic syndrome.
* Thrombocytopenia is typically defined as a platelet count <150,000/microL. Interpretation of a specific abnormal result should be based upon the reference range reported with that result.
¶ Life-threatening pregnancy syndrome includes disseminated intravascular coagulation, preeclampsia, and HELLP (Hemolysis, Elevated Liver enzymes, Low Platelet count).
Δ Worrisome abnormalities of other cell lines include evidence of microangiopathic anemia (schistocytes), immature white blood cells such as blasts, and pancytopenia.
◊ Life-saving interventions should not be delayed while awaiting the results of diagnostic testing.
§ Routine chemistries include electrolytes, blood urea nitrogen, creatinine, and glucose.
¥ Liver biochemical tests include alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin.
‡ Review of the peripheral blood smear by an experienced individual may identify abnormalities not detected by automated machines.

Thrombocytosis/Thrombocythemia



Thrombocythemia/Thrombocytosis

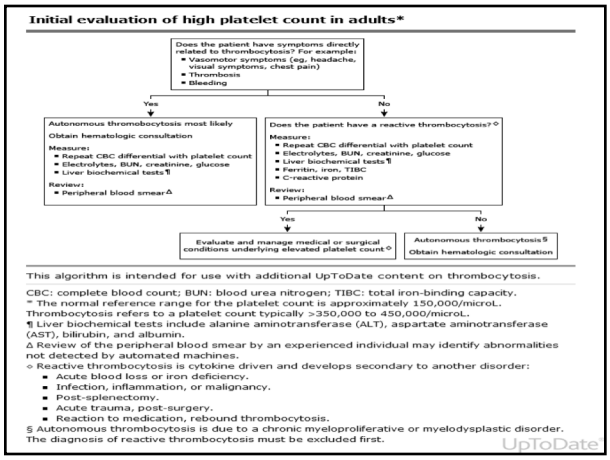
- Thrombocythemia
  - Greater than 450 x 10^9/L
- Types of thrombocythemia
  - Reactive
  - Autonomic

Causes of Thrombocythemia

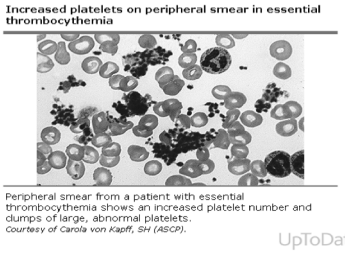
- Reactive Thrombocytosis
  - Anemia
  - Infection
  - Non-infectious inflammation
  - Splenectomy

Causes of Thrombocythemia

- Autonomic thrombocytosis
  - Clonal- means caused by a mutation
    - Myeloproliferative neoplasms (MPN)
      - Essential thrombocythemia
      - Polycythemia vera
      - Myelofibrosis
      - Chronic Myeloid Leukemia
      - Myelodysplastic syndromes
      - Acute myelogenous leukemia

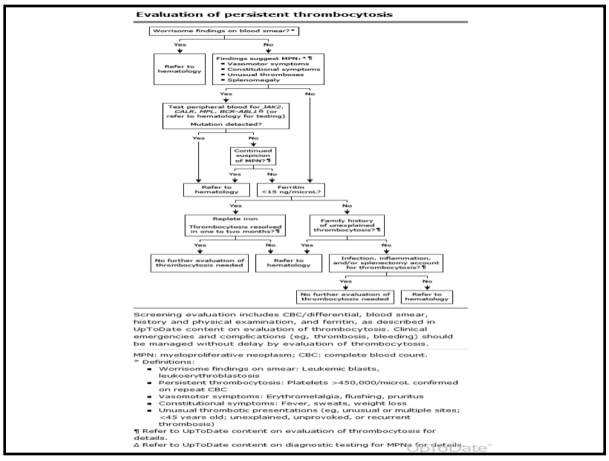


Thrombocythemia



Evaluation of Thrombocythemia

- How quickly to refer depends on:
  - Patient condition
  - Degree of elevated platelets
- Asymptomatic
  - Outpatient
  - Platelets greater than 1 million should be evaluated within days



Referral for thrombocythemia

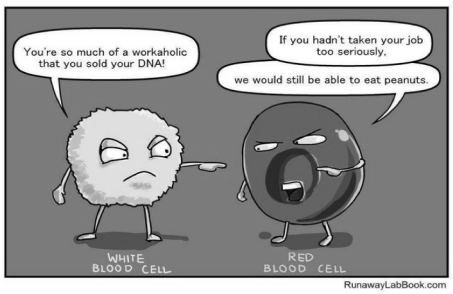
- Reactive thrombocytosis
  - Generally doesn't warrant immediate hematology referral
- Autonomic thrombocytosis
  - Warrants a hematology referral
    - MPN
    - Thrombosis at an unusual site
    - Thrombosis in a young patient less than 45
    - Blasts on peripheral smear

Major causes of reactive thrombocytosis
Nonmalignant hematologic conditions
Acute blood loss
Acute hemolytic anemia
Iron deficiency anemia
Treatment of vitamin B12 deficiency
Rebound effect after treatment of immune thrombocytopenia (ITP)
Rebound effect after ethanol-induced thrombocytopenia
Malignant conditions
Metastatic cancer
Lymphoma
Rebound effect following use of myelosuppressive agents
Acute and chronic inflammatory conditions
Rheumatologic disorders, vasculitides
Inflammatory bowel disease
Celiac disease
Kawasaki disease
Nephrotic syndrome
POEMS syndrome (osteosclerotic myeloma)
Tissue damage
Thermal burns
Myocardial infarction
Severe trauma
Acute pancreatitis
Post-surgical period, especially post-splenectomy
Infections
Chronic infections
Tuberculosis
Acute bacterial and viral infections
Exercise
Allergic reactions
Functional and surgical asplenia
Reaction to medications
Vincristine
Epinephrine, glucocorticoids
Interleukin-1B
All-trans retinoic acid
Thrombopoietin, thrombopoietin receptor agonists
This list is not comprehensive and does not include rare causes of thrombocytosis. Refer to UpToDate and package inserts of potentially implicated medications for further details.

Conclusion

- The Complete Blood Count has so much to offer in terms of diagnosing many medical conditions
- Being aware of diagnosis that affect the CBC can be cost-effective and limit referrals.
- This results in more accurate and concise referrals increasing the optimal patient experience.

The end



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