The CBC: Tips on Interpreting the Most Common Laboratory Test

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American Academy of Physician Associates
Annual Conference
May 20, 2024

Objectives

- Review the complete blood count (CBC) parameters
- Evaluate common abnormalities of the CBC and formulate a differential diagnosis based on results
- Interpret the iron panel and limitations of testing
- Distinguish abnormalities that require evaluation by a specialist

RED CELL FINDINGS

Red blood cells (RBC): total number of erythrocytes per microliter

Hemoglobin (hb or hgb): concentration of hemoglobin grams per deciliter of blood – directly proportional to oxygen-combining capacity of the blood

Hematocrit or packed cell volume (hct, PCV): indirect measure of RBC mass, percentage of volume of packed RBCs in whole blood

RED CELL FINDINGS

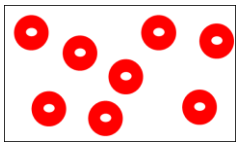
Mean corpuscular volume (MCV): average volume of one erythrocyte in femtoliters

- Low MCV indicates routinely small RBCs – microcytosis
- High MCV indicates routinely large RBCs – macrocytosis
- Normal MCV indicates normal RBCs – normocytic OR indicates a mixture of small and large RBCs

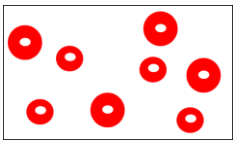
Red cell size distribution width: degree of variation in erythrocyte size, a coefficient of variation

- A high RDW indicates a large variation in size of RBCs

WHAT IS THE MCV AND RDW?



MCV = normal
RDW = normal



MCV = normal
RDW = high

RED CELL FINDINGS

Mean corpuscular hemoglobin: the average weight of hgb per RBC

- How much hemoglobin is carried in each RBC (analogous to weight)
- If someone is iron deficient they will have low MCH because there is not enough hemoglobin (O2 carrying capacity) in the cells

Mean corpuscular hemoglobin concentration: ratio of hemoglobin concentration to volume of erythrocytes

- This is how much hemoglobin is carried in each RBC compared to its size (analogous to BMI)
- If someone is mildly iron deficient, they have a low MCH but the RBCs are also microcytic – therefore the concentration of hemoglobin may still be normal
- Typically elevated if lots of spherocytes

General approach to cytopenia

The patient is either…

1. Not making it
   - Bone marrow suppression/failure
2. Destroying it
   - Immune destruction, iatrogenic
3. Losing it
   - Bleeding, abnormal storage

Anemia

Microcytic	Normocytic	Macrocytic
Iron deficiency Lead poisoning Thalassemias Sideroblastic anemias Chronic inflammation Hypoproteinemia	Acute/Chronic inflammation or infection Bone marrow suppression Congenital/Acquired hemolytic anemias Acute/Subacute blood loss Hypersplenism/Splenic sequestration Transient erythroblastopenia of childhood (TEC)	Reticulocytosis Vitamin B12 or Folate deficiency Diamond Blackfan Anemia Bone marrow failure Liver disease Hypothyroid Iatrogenic Normal newborn

Taken from *The Bethesda Handbook of Clinical Hematology*

Anemia

Symptoms

- History is important because PE findings are minimal and subjective
- Bleeding: quantify menstrual loss, bloody urine/stool
- General: Fatigue, poor concentration, palpitations, headache, shortness of breath on exertion, dizziness/lightheadedness, changes in appetite/sleep, irritability
- Iron deficiency: Pica (ice, dirt, paper, hair, cloth)
- Severity of low Hgb/Hct doesn't always predict severity of symptomology

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Anemia

Physical Exam

- General: pallor, systolic murmur, tachycardia, hypotension
- Iron deficiency: brittle nails, spooning nails (koilonychia)
- B-12 deficiency: smooth tongue (glossitis)
- Hemolytic: jaundice, icterus, dark urine (hemoglobinuria)

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Anemia

Work Up – Testing

- Laboratory – CBC, reticulocyte count, blood smear
  - Further testing based on these results
- FOBT (fecal occult blood test), aka stool guaiac
- Imaging – Upper/lower endoscopy, Pelvic ultrasound
- Bone marrow aspiration/biopsy
  - Presence of other cytopenias

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Anemia

Treatment

- Therapy depends on underlying etiology
  - Stop bleeding
  - Fix nutritional deficiency
- PRBC transfusion
  - Acute blood loss or *hemodynamic instability*
  - Patient dependent

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Anemia of Chronic Inflammation

- Usually mild anemia that is normo/microcytic and normochromic with a normal reticulocyte count
- Typically an indication of an underlying chronic or inflammatory condition
- The anemia itself typically corrects with treatment of the underlying condition
- Some conditions are difficult to treat and anemia can persist
- Rule out other causes of anemia if appropriate – especially vitamin deficiencies

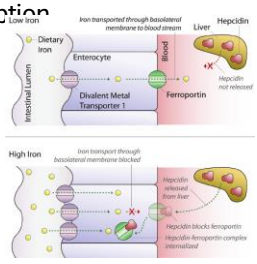
Anemia of Chronic Inflammation

- Common with autoimmune diseases and may be the first laboratory finding
  - Systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease
- Congenital disorders
  - Cystic fibrosis
- Organ specific disease
  - Kidney, thyroid, pituitary, liver
- Infections
- Malignancy

The Iron Panel in Iron Deficiency

- Initially serum ferritin is utilized and becomes decreased
  - Transferrin brings iron to marrow to be utilized in synthesizing new erythrocytes
- Serum iron decreases
- Transferrin concentration increases as the body is trying to find all the iron possible
- Transferrin saturation decreases because there is nothing to saturate the transferrin
- Total iron binding capacity (TIBC) increases
  - Patient's blood + iron ex vivo, then count how much iron binds – it will bind excessively because the blood is so hungry for iron and the transferrin is unsaturated
  - Basically, TIBC is the inverse of transferrin saturation

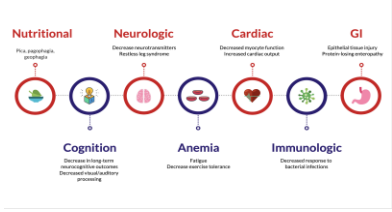
Iron Absorption



↑ Hepcidin with High Serum Fe Inflammation

Nagpawalla OZ, Webb JA, Giger U. Iron deficiency anemia. Can Vet J. 2012 Mar;53(3):230-6. PMID: 22942459

Iron deficiency is more than just anemia



Adapted from: Powers JM, Buchanan G. Hematol Oncol Clin North Am. 2014 Aug;28(4):729-45. 2014 Jun 2

Vitamin B12 and Folate Deficiencies

Both can cause macrocytic anemia

At risk populations

- B12: Vegans, s/p gastric bypass, pernicious anemia, inborn errors of metabolism, IBD, parasites
- Folate: Meat eaters, folate inhibiting medications, alcohol abuse

Consequences of deficiency

B12: macrocytic anemia, pancytopenia, neurologic deficits

- Elevated methylmalonic acid (MMA) +/- elevated homocysteine

Folate: neural tube defects (in pregnant women), early cardiovascular disease, malignancy

- Elevated homocysteine

Don't check folate without checking B12

Hemolytic Anemia

Hemolysis is the breakdown of RBCs

Hemolytic anemia is the resulting RBC imbalance due to excessive hemolysis

- Defective RBC
  - Membrane (hereditary spherocytosis [HS]), enzyme systems (G6PD Deficiency, pyruvate kinase [PK] deficiency), hemoglobin (sickle cell disease, thalassemia)
- Break down due to external factors
  - Immune/autoimmune destruction (autoimmune hemolytic anemia [AIHA])
  - Microangiopathic (thrombotic thrombocytopenic purpura [TTP], hemolytic uremic syndrome [HUS], mechanical cardiac valve
  - Infection (malaria, clostridium, borrelia)
  - Other: hypersplenism, burns

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Hemolytic anemia

Laboratory Considerations

- In general, all hemolytic anemias should have:
  - Elevated reticulocyte count, decreased haptoglobin*
- Most will have:
  - Increased LDH or plasma hemoglobin (intravascular hemolysis)
  - Increased indirect bilirubin (extravascular hemolysis, causes jaundice/icterus)
  - Spherocytes (generally present, HS, AIHA), schistocytes (cut RBCs, in TTP and HUS)

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Approach to Leukopenia

- Determine which specific leukocyte is decreased
  - Neutropenia: unusual or recurrent bacterial/fungal infections, mucocutaneous ulcers
  - Lymphopenia: recurrent URIs, "bad allergies," poor vaccine response
- If no lines are significantly low, options include repeating labs, observation

Neutropenia

Defined as an absolute neutrophil count (ANC) <1500/µL

Typically referred to as

- Mild: ANC 1000-1500
- Moderate: ANC 500-1000
- Severe: ANC <500
  - Agranulocytosis: <200

What does a neutrophil do?

- *Primary* cell in immune response to pyogenic organisms and *predominate* cell in acute inflammatory infiltrates
- Neutropenia increases susceptibility to bacterial and fungal infections
  - Skin and oral cavity most commonly affected
  - Sepsis is a common complication resulting in morbidity and mortality
  - S/sx of infection may be altered with neutropenic patient

Common Causes of Neutropenia

Infection/Viral suppression → #1 cause of transient neutropenia in kids
Drug-induced (antibiotics, antiepilectic drugs, psychotropic agents)
Autoimmune Neutropenia → #1 cause of chronic neutropenia in kids
Duffy null phenotype (aka benign ethnic neutropenia)
Immune dysfunction (autoimmunity, congenital immunodeficiencies, HIV)
Neonatal causes (prematurity, alloimmune)
Metabolic disorders (Barth Syndrome, glycogen storage disease 1b)
Nutritional deficiencies (vitamin B12, copper)
Bone marrow failure/infiltration (leukemias, sever congenital neutropenia)

Duffy Null RBC

A BENIGN mild-moderate neutropenia, more common in certain ethnic groups
- Can be found in any ethnicity
- Prevalence estimated at 10-30%
- Otherwise normal leukocytes
- No history of abnormal or recurrent infections
- NO INCREASED RISK OF LOCAL OR SYSTEMIC INFECTIONS
- Does not require specialist care
- Blood typing for Duffy antigen

Hsieh, M, Everhart, JE, et al. *Prevalence of Neutropenia in the U.S. Population: Age,Sex, SmokingStatus, and Ethnic Differences*. Ann Intern Med. 2007;146:486-492.

Lymphopenia

Lymphocytes (T cells, B cells, NK cells, NKT cells)
- Primary cell of specific immune recognition
- Differentiate self vs non-self (T_{reg})

Lymphopenia – often in rheumatologic diseases, iatrogenic
- T cells: CD4+ <200
  - PJP prophylaxis
- B cells: produce immunoglobulins
  - May be treated with IVIG

Thrombocytopenia

- Platelets are responsible for primary hemostasis and wound healing
  - Normal platelet count is >150,000/µL
  - Bleeding due to thrombocytopenia is typically mucocutaneous
    - Oral, GI, GU, skin
- Moderate-severe bleeding and petechiae typically occur with counts <20,000/µL

Thrombocytopenia

Newborn
- Infection, infection, infection
- Maternal factors (preeclampsia, medications, etc)
- Neonatal alloimmune thrombocytopenia (NAIT)

Immune thrombocytopenia (ITP)

Autoimmune disease/immunologic disorder

Inherited platelet/bone marrow disorders (MYH9, telomere disease)

Iatrogenic

Pseudothrombocytopenia/lab error

Thrombocytopenia

Treatment
- >30,000/µL – typically observed
- Severe or associated with bleeding
  - Lack of platelet production – platelet transfusion
  - Platelet destruction – immune suppression or stimulate production
    - ITP - IVIG, steroids, thrombopoietin-receptor agonists
  - Liver disease - thrombopoietin-receptor agonists

Pancytopenia

Acquired aplastic anemia (AA)
- Usually ≥2 cytopenias, often moderate to severe, normal/high MCV

Inherited bone marrow failure syndrome (IBMFS)
- Presents with 1-3 cytopenias, often macrocytic
- Most have an increased risk of acute myeloid leukemia (AML) and/or other cancers throughout lifetime
- Associated with other syndromic features

Malignancy
- Most frequently leukemias

Erythrocytosis

- Elevated hemoglobin (or hematocrit)
- May or may not be related to underlying blood disorder
  - Malignancy – erythropoietin secreting tumor
  - Physiologic – increased testosterone, hypoxic states
  - Inherited – abnormal hemoglobins
- Some etiologies have an increased risk of thromboembolism

POLYCYTHEMIA vERA

- One of a group of disorders termed chronic myeloproliferative neoplasms (MPN)
  - Not dysplastic – hematopoiesis is normal and effective
  - MPNs: essential thrombocytosis (ET), myelofibrosis with myeloid metaplasia (MMM), chronic myelogenous leukemia (CML), chronic myelomonocytic leukemia (CMML)
- Leukemic transformation is possible
- JAK2 (JAK2V617F) mutation is commonly found, but not necessarily diagnostic (90% with mutation)

Thrombocytosis

Causes
- Trauma/Fracture
- Sudden Exercise
- Inflammatory disorders (rheumatoid arthritis, ulcerative colitis)
- Iron deficiency
- Post-splenectomy
- Myeloproliferative Neoplasms

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Essential Thrombocythemia

- Elevated platelet count in absence of other causes
  - Normal red blood cell mass/hematocrit
  - Absence of Philadelphia Chromosome
  - Associated with JAK2 mutation
- Age of Onset: 50-60 years
- Bleeding and thromboembolism can occur in platelet count over 1,000,000 uL
  - Qualitative platelet defect
  - Acquired Von Willebrand

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Eosinophils and Basophils

Particularly good at fighting multicellular organisms

Primary cells in atopic disorders

Eosinophilia (absolute eosinophil count >500):

500-1000: Allergies, asthma

>1500: Parasitic infections, malignancies, rheumatologic disorders, immunodeficiencies, hypereosinophilic syndrome

Basophilia:

Hypersensitivity reactions, anaphylaxis, infections, chronic myelogenous leukemia (CML)