Decoding the CBC

Jill MacPherson DNP, APRN, FNP-BC, AOCNP

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

• What 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

Disclosures

None
Hematology

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

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Hematopoietic stem cells

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

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Stem cell function

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

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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

- Normal Neutrophils
  - Approximately between $1.5 \times 10^9/L$-$6.5 \times 10^9/L$
  - At birth normal is approximately $12 \times 10^9/L$
- Neutropenia
  - $<0.5 \times 10^9/L$ [500/μL]
- Neutrophilia
  - $>7.5 \times 10^9/L$ (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
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

Eosinophils and/or Basophilia

- Infection
- Parasitic
- Allergies
- Cancer
**Eosinophils**

The peripheral blood smear on the left shows a low-counted eosinophil, one of our leukocytes. Eosinophils normally are much lower in number than other leukocytes. Eosinophils granulate, releasing enzymes during an allergic reaction, as indicated by the red arrow on the right. A woman age 62 years old with hypereosinophilic syndrome and a severe case of eosinophilia developed a high heart rate. The eosinophil shown marked hypereosinophilia.

**Basophils**


**Monocytes**

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

**Infection**

**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

**Acute Myeloid Leukemia**

Peripheral smear from a patient with acute myeloid leukemia.

Monocytes with JNer rash in 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

Chronic Lymphocytic Leukemia

Lymphocytes

- Lymphopenias<-1.0X10^9/L
  - Immune deficiency
  - 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

Lymphoma

- Drug induced Lymphocytosis
  - Dasatanib
  - Ibrutinib

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

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

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

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: Normal platelets (arrowshead) and a normohemochytic erythrocyte cell also shown. The red cells vary in size (normochromic normocytic), and there are no abnormalities such as spherocytes, poikilocytes, or macrocytes. The line of demarcation of the small lymphocytes central paler (dashed arrow) should equal one third of its diameter.

Anemia

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

Iron deficiency

Normal values for red blood cell parameters in adults

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean (Normal)</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>14.0-17.5 g/dL</td>
<td>9.0</td>
<td>20.0</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>40-50%</td>
<td>24%</td>
<td>65%</td>
</tr>
<tr>
<td>RBC (count)</td>
<td>4-5.5 x 10^6</td>
<td>2.5</td>
<td>6.5</td>
</tr>
<tr>
<td>Mean corpuscular volume (MCV)</td>
<td>75-100 fL</td>
<td>60</td>
<td>120</td>
</tr>
<tr>
<td>Mean cell hemoglobin (MCH)</td>
<td>27-31 pg</td>
<td>13</td>
<td>45</td>
</tr>
<tr>
<td>Mean cell hemoglobin concentration (MCHC)</td>
<td>32-36 g/dL</td>
<td>25.5</td>
<td>42</td>
</tr>
<tr>
<td>Red cell distribution width (RDW, CV, skewness)</td>
<td>12.0%</td>
<td>10.0%</td>
<td>14.0%</td>
</tr>
</tbody>
</table>

Kinetic Approach

Iron deficiency

Morphologic Approach

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

MCV: mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, RDW: red cell distribution width.
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

Macro-ovalocytosis in vitamin B12 deficiency

- Megaloblastic anemia
- Big irregular erythrocytes

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

- Basophilic stippling of red cells in lead poisoning

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

Courtesy of Cagan von Kattat, MD, PhD.
Sickle Cell Anemia

Abnormal red blood cells

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?

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

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

Causes and mechanism of macrocytosis

<table>
<thead>
<tr>
<th>Causes and mechanisms of macrocytosis</th>
<th>Macrocytic anemia</th>
</tr>
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<tbody>
<tr>
<td>Hematopoietic disorders</td>
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<td>MDS</td>
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<tr>
<td>Multiple myeloma and other plasma cell disorders</td>
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</table>
Polycythemia (erythrocytosis)

- Polycythemia is:
  - Increased hemoglobin concentration
    - Greater than 16.5 g/dl for men
    - Greater than 16.0 g/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
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
    - 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

Causes of polycythemia

- Red cell mass increase
  - Increased production (erythroblastic, myelodysplastic, hereditary)
  - Decreased destruction (hemolytic anemia, renal failure)

Types of polycythemia

- Primary (essential)
  - Essential polycythemia
  - Essential thrombocytemia
- Secondary
  - Hypoxemia
  - Increased EPO levels
  - Cigarette smoking
  - Exposure to carbon monoxide
  - Use of androgens
  - Use of erythropoietic agents

Hyper-viscosity symptoms

- Thrombosis or bleeding
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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
    - Vitamin 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 X 10^9/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

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

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
Thrombocytosis/Thrombocytemia

- Greater than 450 x 10^9/L

Types of thrombocytemia
- Reactive
- Autonomic

Causes of Thrombocytemia

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

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

Causes of Thrombocytemia

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Initial evaluation of high platelet count in adults

1. Anemia
2. Infection
3. Non-infectious inflammation
4. Splenectomy
5. Peripheral blood smear
6. Myeloproliferative neoplasms

Causes of Thrombocytemia

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Thrombocytemia

Increased platelets on peripheral smear in essential thrombocythemia

Peripheral smear from a patient with essential thrombocythemia shows an increased platelet number and clumps of large, abnormal platelets.

*Courtesy of Samuel van Vlaardingen, MD, PhD.*
**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

**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.

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**The end**

- You're no match for a workaholic, that you said your DMA.
- If you hadn't taken your job too seriously, we could still be able to eat salad.