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RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

Inaugural National Conference

December 3 – 5, 2020

VIRTUAL CONFERENCE

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RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

Hematology

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Faculty Disclosures

Beth Faiman, PhD, MSN, APRN, BC, AOCN®, FAAN

- There are currently no relationships to disclose.

Objectives

- In this workshop we will review:
  - Normal and abnormal hematopoiesis
  - Common (and less common) blood disorders
  - Malignant blood disorders

What Is Hematology?

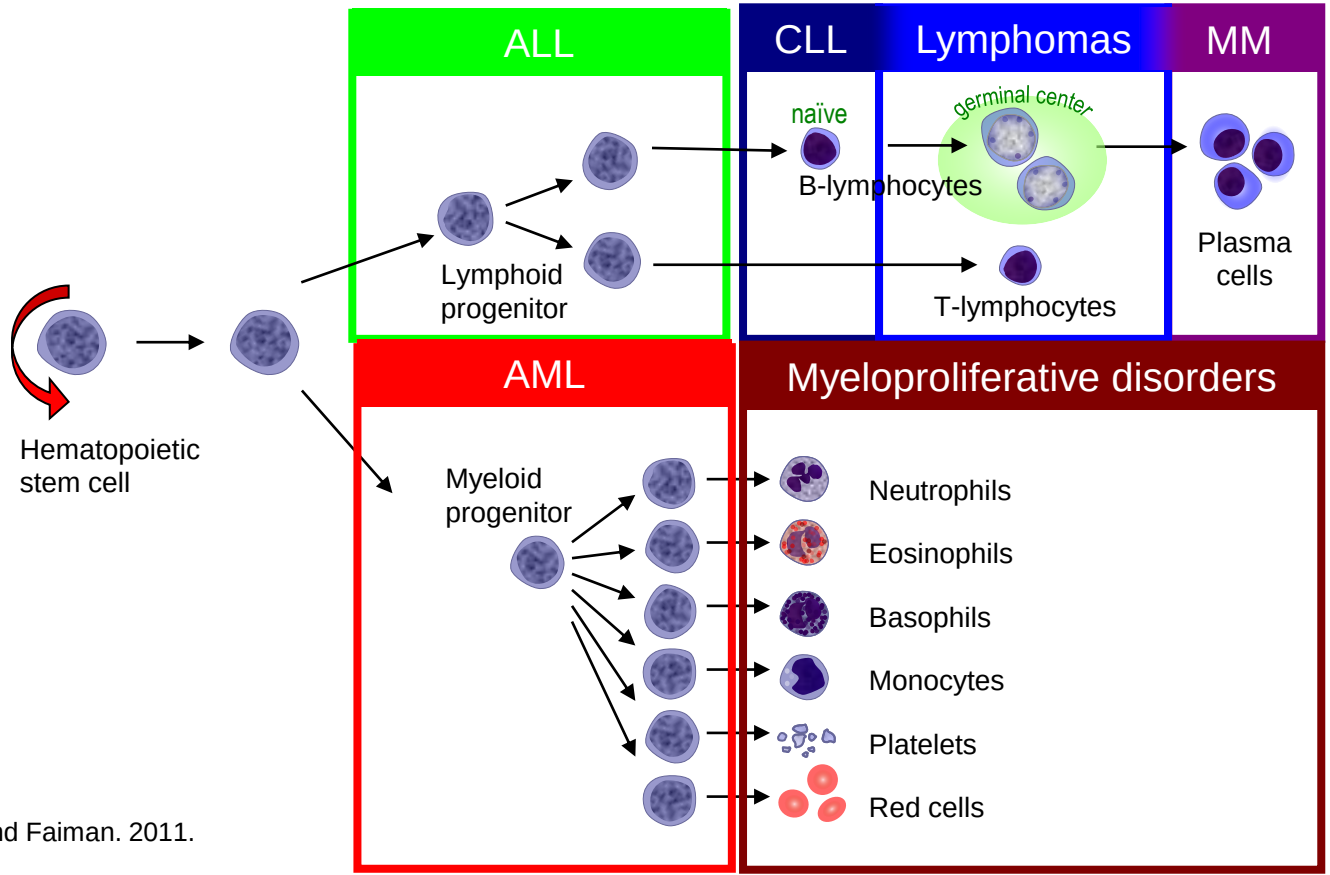
- The study of the normal and pathologic aspects of blood and blood elements
- The cellular elements that arise from the hematopoietic stem cell normally circulate in blood
  - Red blood cells (RBCs),
  - Platelets
  - White blood cells (WBCs)
    - Neutrophils, monocytes, lymphocytes, eosinophils, basophils

Numerous Benign Heme Disorders

- Iron deficiency anemia
- Megaloblastic anemia (vitamin B12 and folic acid deficiency)
- Congenital hemolytic anemia
- Thalassemias
- Sickle cell disease
- Hemolytic anemia
- Paroxysmal nocturnal hemoglobinuria (PNH)
- Factor VIII deficiency (hemophilia A)
- Factor IX deficiency (hemophilia B)
- Factor XI deficiency (hemophilia C)
- Factor V, X, and II disorders
- Factor XIII deficiency
- Von Willebrand Disease
- Waldenstrom Macroglobulinemia
- Transfusion therapy

- Disseminated Intravascular Coagulation (DIC)
- Thrombocytopenia
- Immune Thrombocytopenia Purpura (ITP)
- Thrombotic Thrombocytopenia Purpura (TTP)
- Hemolytic Uremic Syndrome (HUS)
- Primary Thrombocytosis
- Thrombosis
- Cancer Associated Thrombosis
- Neutrophilia
- Neutropenia
- Chediak-Higashi syndrome (CHS)
- Leukocyte adhesion deficiency
- Eosinopenia
- Eosinophilia
- Monocytopenia
- Monocytosis
- Aplastic Anemia
- Monoclonal Gammopathy of Unknown Significance (MGUS)

Normal and Abnormal Stem Cell Development



Tariman and Faiman. 2011.

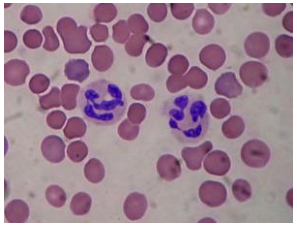
Erythrocytes (RBCs)

- Non-nucleated cells that package **hemoglobin**, the protein that carries oxygen to and carbon dioxide from tissues.
- Erythropoiesis is regulated by the growth factor **erythropoietin** and takes 4 days.
- Reticulocyte counts reflect the percentage of early RBCs in the total number of RBCs in the circulation. Normal count: less than 2%.
- RBC lifespan is 120 days.

Camaschella C. Iron deficiency: new insights into diagnosis and treatment. Hematology Am Soc Hematol Educ Program. 2015;2015:8-13. doi: 10.1182/asheducation-2015.1.8. PMID: 26637694;
Mithoowani S, Laureano M, Crowther MA, Hillis CM. Investigation and management of erythrocytosis. *CMAJ*. 2020 Aug 10;192(32):E913-E918. doi: 10.1503/cmaj.191587. PMID: 32778603.
http://criticalcaredvm.com/wp-content/uploads/2015/03/6-red-blood-cells-sem-susumu-nishinaga.jpg.

Neutrophils

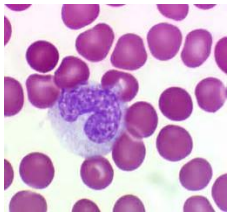
- Nucleus that is usually a 3- or 4-lobed structure and stains a bluish color.
- An early form of a neutrophil is a band that shows an unsegmented neutrophil.
- Role: phagocytize and digest bacteria, cellular debris, and dead tissue.
- Normally takes 12-13 days to be produced in bone marrow.
- Lifespan in the circulation: About 12 hours, but it can live in tissues for several days.
- Only half of the neutrophils that are circulating are reflected in the WBC count. In adults, they constitute 50-80% of the total WBC counted.



Rosales C. Neutrophils at the crossroads of innate and adaptive immunity. *J Leukoc Biol*. 2020 Jul;108(1):377-396. doi: 10.1002/JLB.4MIR0220-574RR. Epub 2020 Mar 23. PMID: 32202340.

Monocytes

- Large, mononuclear cells with an indented nucleus (kidney shaped).
- Host defense against organisms while in the circulation (similar to that of neutrophils).
- Spend 1-3 days in the bone marrow and 8-72 hours in the peripheral blood.
- Once they traverse into tissues, they can differentiate into macrophages, and survive in tissues for long periods (up to 80 days).



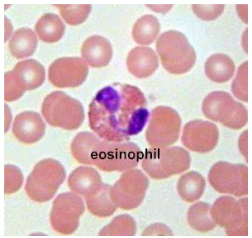
LEUNG, l. (2020) Approach to patient with Anemia. https://www.uptodate.com/contents/approach-to-the-adult-with-anemia.

Macrophages

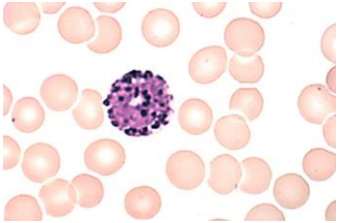
- Macrophages are characterized by and named for their tissue origin (e.g., alveolar macrophages in lungs, Kuppffer cells in liver, splenic macrophages, and oligodendrocytes or glial cells in the brain.
- Role of macrophages: *phagocytize pathogens, cellular debris, and dead tissue.*

Eosinophils

- Prominent reddish orange granules, usually have bilobed nuclei
- Increase the reaction to foreign proteins |(seen in parasitic infections, allergic conditions, cancer, and certain drugs)
- Normally, constitute 0%-2% of WBC count

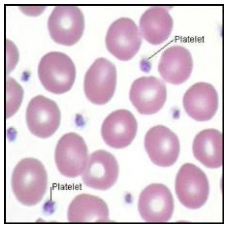


Basophils



- Colorful cells with very dark bluish prominent granules
- Granules contain histamine, heparin, and hyaluronic acid
- Histamine release (basophil degranulation) is part of allergic reactions
- Normally, basophils constitute 1% of the WBC count. Higher counts are often higher in patients with myeloproliferative disorders

Platelets



- Nonnucleated cell fragments that contain messenger RNA
- Derived from the cytoplasm of the bone marrow megakaryocytes; growth regulated by thrombopoietin
- Lifespan: 8-10 day; first 1-2 days in the spleen.
- Platelets can be entrapped by an enlarged spleen, as seen in congestive or inflammatory disorders.
- Play an important role in hemostasis because they contain many hemostatic cofactors and inhibitors in their granules.

Thrombocyte lifespan. Accessed on November 17, 2020 from https://www.sciencedirect.com/topics/biochemistry-genetics-and-molecular-biology/thrombocyte-lifespan.

The Complete Blood Count: Cytopenias

- Leukopenia
- Neutropenia
  - Granulocyte percentage
  - Absolute granulocyte
- Thrombocytopenia

Lab/Normal Reference Range	Value
WBC: 4.0–11.0 k/uL	1.92
Plt: 150–400 k/uL	209
MPV: 9.0–12.7 fL	9.4
Neutrophil: 38.5%–75.0%	48.0 (L)
Absolute neutrophil: 1.00–7.50 k/uL	0.92 (L)
Lymphocyte: 15.9%–47.3%	35.5
Absolute lymphocyte: 1.00–4.00 k/uL	1.69

❖ Lab values vary slightly amongst institutions and laboratories.

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Evaluation of Anemia

Mechanisms of Anemia

1. *Bleeding:* The loss of RBCs (GI tract, menstruation)
2. *Increased destruction:* a shortened RBC survival time not explained by bleeding (hemolysis)
3. *Decreased production* of RBCs from underlying causes
   - Nutritional deficiencies (iron, vitamin B12, folic acid, copper, zinc)
   - Kidney disease
   - Anemia of chronic disease
   - Primary bone marrow disorder (Myelodysplasia, leukemia, aplastic anemia)

Sankaran V. G., & Weiss M. J. 2015. Anemia: progress in molecular mechanisms and therapies. *Nature Medicine.* 21(3), 221–230. https://doi.org/10.1038/nm.3814.

The Complete Blood Count: Anemia (Cont.)

- Workup for anemia
  - LDH
  - Monoclonal Protein
  - Haptoglobin, coombs
  - Retic
  - Iron studies (Iron+Tibc, Ferritin)
  - TSH
  - EPO
  - B12, MMA
  - Folate
  - Zinc/Copper??
  - CRP/ESR
  - BUN/Cr
  - Hb electrophoresis
  - H. Pylori if sx and IDA
- Lab values vary slightly amongst institutions and laboratories

Lab/Normal Reference Range	Value
Ferritin: 18.0–300.0 ng/mL	22
TIBC: 210–415 ug/dL	440
Iron: 30–140 ug/dL	99
Folate: 2–18 ng/mL	> 18
MMA: 79–376 nmol/L	**399**
Vitamin B12: 221–700 pg/mL	**200**

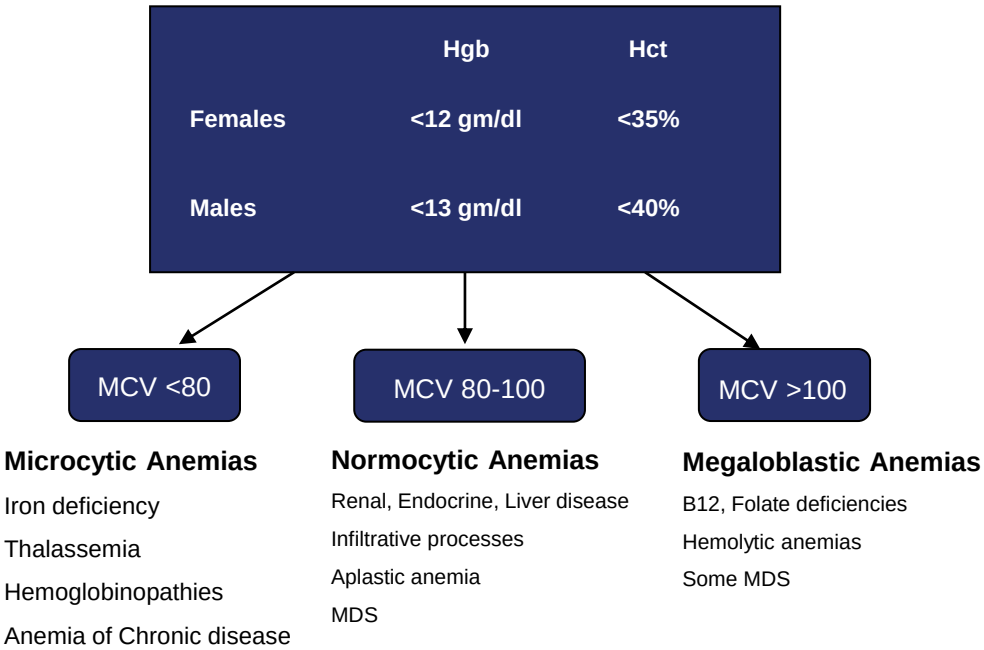
Overview of Hematologic Cancers. December 4, 2020 l 19.
TIBC = total iron binding capacity; MMA = methylmalonic acid.
NCCN. 2020; Sankaran V. G., & Weiss M. J. (2015). Anemia: progress in molecular mechanisms and therapies. *Nature Medicine.* 21(3), 221–230. https://doi.org/10.1038/nm.3814

Evaluation of Anemia: Normal Test Ranges

Laboratory Test	Normal Value
Red blood cell count	Male: 4.7–6 million cells/mcl; female: 4.2–5.4 million cells/mcl
Hemoglobin	Male: 13.5–18 g/dl; female: 12–16 g/dl
Hematocrit	Male: 42%–52%; female: 37%–47%
Mean corpuscular volume	78–100 fL
Mean corpuscular hemoglobin	27–31 pg/cell
Red cell distribution width	11.5%–14%
Reticulocyte count	0.5%–1.85% of erythrocytes
Ferritin	Male: 20–300 ng/ml; female: 15–120 ng/ml
Serum iron	Male: 75–175 mcg/dl; female: 65–165 mcg/dl
Total iron-binding capacity	250–450 mcg/dl
Serum erythropoietin level	Male: 17.2 mU/ml; female: 18.8 mU/ml
Coombs test (direct and indirect)	Negative
Serum B_{12}	190–900 ng /ml
Serum folate	> 3.5 mcg/L

Overview of Hematologic Cancers. December 4, 2020 l 20.
Table 111-1. Laboratory Assessment of Anemia: Normal Values (Adults) Faiman, 2013.
Clin Manual for APNs. ONS publishing.

First, Check the Size of the RBC (MCV)



Turner J, Parsi M, Badireddy M. *Anemia*. [Updated 2020 Sep 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499994/.

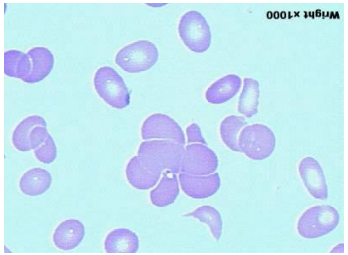
Next, Look at Reticulocyte Count

- Young erythrocytes
- In an anemia, the reticulocyte% must be corrected for the severity of anemia to obtain reticulocyte production index
- **Elevated**: suggests RBC loss (bleeding) or destruction
- **Normal or decreased**: defective production of RBCs, acute blood loss, RBC destruction, vitamin or mineral deficiency, bone marrow depression (drugs, chronic infection, chronic inflammation, malignancy), and defective RBC production (kidney disease, myelodysplastic syndrome, pure red cell aplasia, lead poisoning, and alcoholism)

Turner J, Parsi M, Badireddy M. *Anemia*. [Updated 2020 Sep 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499994; Reticulocyte calculator. Available: https://www.mdcalc.com/absolute-reticulocyte-count-reticulocyte-index.

Macrocytic Anemia
MCV > 100

- **Elevated Retics**
  - Autoimmune hemolytic anemia
  - Cold agglutinins
  - Non-immune hemolysis
  - Acute blood losses



- **Low or semi-normal**
  - B12 deficiency
  - Folate deficiency
  - MDS
  - Aplastic anemia
  - Hypothyroidism
  - Drugs that cause macrocytosis, e.g. Etoh, HIV drugs, TMP/Sulfa

Camaschella C. Iron deficiency: new insights into diagnosis and treatment. *Hematology Am Soc Hematol Educ Program*. 2015;2015:8-13. doi: 10.1182/asheducation-2015.1.8. PMID: 26637694.

Serum Vitamin B12 Level

- Some situations may lead to levels that are falsely low (folate deficiency, pregnancy, oral contraceptives), elevated (liver disease, CML), or normal
- **Homocysteine level**: when elevated, can mean either vitamin B12 or folic acid deficiency
- **Methylmalonic acid**: elevated only in patients with vitamin B12 deficiency

Turner J, Parsi M, Badireddy M. *Anemia*. [Updated 2020 Sep 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499994/.

Treatment Deficiency

Treatment B12 Deficiency: -1 mg IM daily for 3-7 days; 1 mg IM weekly for 4-8 weeks, then 1 mg IM monthly for life

- Can also be given orally (sublinqual)

Treatment Folic Acid Deficiency: Oral is typically used 1-5 mg daily

- Given prophylactically in women contemplating pregnancy to prevent neural tube defects, pregnant or lactating women, and patients with chronic hemolysis and increased erythropoiesis
- Elevated homocysteine levels have been associated with an increased risk for cardiovascular disease, so these patients should be treated with folic acid (decreases homocysteine levels)

Turner J, Parsi M, Badireddy M. *Anemia*. [Updated 2020 Sep 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499994/.

Microcytic Anemia
MCV < 80

- Iron deficiency the most common
  - MCHC also low as well as MCV
- Thalassemias
  - Alpha – needs DNA studies (Alpha Thal gene deletion)
  - Beta – Hgb HPLC/electrophoresis; Hgb A2↑
- Hemoglobinopathies
- Anemia of Chronic inflammation/disease
- Sideroblastic anemia

Turner J, Parsi M, Badireddy M. *Anemia*. [Updated 2020 Sep 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499994/

Iron Deficiency Anemia: Overview

- Ferritin is the major storage form of iron, sequestered in a nontoxic form and available for future use.
- The metabolism of iron is dominated by its role in hemoglobin synthesis.
- **Metabolism:** Iron is absorbed from the duodenum and proximal jejunum in the GI tract or modified from iron stores in the liver. It then enters the plasma, where it is bound to transferrin. The circulating iron is transported from the plasma to cells that have the capacity to make Hgb in the bone marrow.
- Colonoscopy/EGD if anemia suspected.

Turner J, Parsi M, Badireddy M. *Anemia*. [Updated 2020 Sep 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499994/.

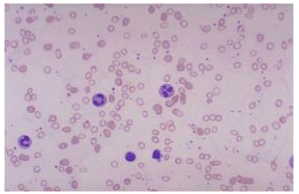
Iron Excretion

- No physiologic mechanism for iron excretion
- Iron is lost from the body only when cells are lost, especially epithelial cells in the GI tract, skin, and renal tubles
- Normally, 1-2 mg of iron is lost each day
- Menstruating women lose an additional 0.006 mg/kg/day of iron (on average) prorated over the entire menstrual cycle-more with menorrhagia!
- Pregnant women lose iron at a rate approximately 3.5 times that of normal men (goes to fetus)

Iron Deficiency Anemia. On-line. Accessed on 11/17/2020 rom https://www.hematology.org/education/patients/anemia/iron-deficiency.

Etiology of Iron Deficiency

A number of clinical situations can lead to iron deficiency:



- Increased iron requirements due to physiologic stresses (growth, pregnancy, lactation)
- Increased iron requirements due to pathologic causes (blood loss)
- Inadequate iron supply (consumption of foods low in iron, impaired absorption of iron, abnormal transferrin function)

Turner J, Parsi M, Badireddy M. *Anemia*. [Updated 2020 Sep 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK499994.

Testing for Iron Deficiency

Leads to other answers for microcytosis

Ferritin	N/↑	N/↑	Low	High	N
Serum Iron	N/↑	Low	Low	High	N
TIBC	N	N/Low	High	Low	N
% Sat	N	Low/N	Low	High	N
Dx or next?	Thal Hgb electrophoresis	Inflam; chr disease	Iron def	**Sidero-blastic**	Hgb problem; Hgb electro-phoresis

Oral Iron Repletion

- Ferrous salts absorbed better than ferric
  - Ferrous sulfate ~65mg elemental iron daily; 1 tablet of the standard 324mg preparation
  - Ferrous gluconate, ferrous fumarate, iron polysaccharide
  - Not enteric-coated

- Absorption in duodenum; best with acidic environment & fasting
- Treat for 3-6 months AFTER CBC has normalized
- Side effects: constipation, GI upset, nausea, sometimes diarrhea

Santiago P. (2012). Ferrous versus ferric oral iron formulations for the treatment of iron deficiency: a clinical overview. *The Scientific World Journal.* 2012, 846824. https://doi.org/10.1100/2012/846824.

Parenteral Iron Therapy

- Failure of oral therapy; severe losses; malabsorption esp Roux-en-Y bypass
- Iron dextran – 25mg test dose; can give up to 1 gram in normal saline over 4-5 hours
- Ferric sucrose (Venofer), ferric gluconate (Ferrlecit), ferumoxytol (Feraheme), ferric carboxymaltose (Injectafer)
  - No test dose;100mg to max 750 mg/day
  - Large doses can cause acute iron toxicity
- Side Effects: fever, HA, myalgia/arthralgia, anaphylactic shock

A Classic Iron Deficient Patient

- 42 YO w/ psoriatic arthritis
- Increased fatigue; diagnosed with iron def anemia 2016
- Placed on oral iron for 2 months then stopped due to side effects of constipation
- Due to fatigue, counts rechecked in May 2017:
- **Treatment**: IV iron
- Injectafer 750 mg weekly x 2 (1500 mg total)
- Reassess 8 weeks post last iron infusion

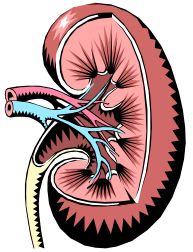
Laboratory Results

Component	Latest Ref Rng & Units	4/23/2016	8/9/2016	5/10/2017
WBC	3.70 - 11.00 k/uL	7.07	7.80	9.90
RBC	3.90 - 5.20 m/uL	4.29	4.44	4.07
Hemoglobin	11.5 - 15.5 g/dL	**8.4 (L)**	11.5	**7.7 (L)**
Hematocrit	36.0 - 46.0 %	**29.5 (L)**	37.1	**27.5 (L)**
MCV	80.0 - 100.0 fL	**68.8 (L)**	83.6	**67.6 (L)**
MCH	26.0 - 34.0 pG	**19.6 (L)**	**25.9 (L)**	**18.9 (L)**
MCHC	30.5 - 36.0 g/dL	**28.5 (L)**	31.0	**28.0 (L)**
RDW-CV	11.5 - 15.0 %	**19.3 (H)**	**17.3 (H)**	**19.8 (H)**
Platelet Count	150 - 400 k/uL	**427 (H)**	362	**496 (H)**
MPV	9.0 - 12.7 fL	9.3	9.8	9.5
Neut%	%	62.7		61.4
Abs Neut (ANC)	1.45 - 7.50 k/uL	4.43		6.08
Lymph%	%	21.2		28.2
Abs Lymph	1.00 - 4.00 k/uL	1.50		2.79
Mono%	%	10.3		6.3
Abs Mono	0.00 - 0.86 k/uL	0.73		0.62
Eosin%	%	5.2		3.4
Abs Eosin	0.00 - 0.45 k/uL	0.37		0.34
Baso%	%	0.6		0.7
Abs Baso	0.00 - 0.10 k/uL	0.04		0.07
Nucleated Reds	0 /100 WBC			0.0
NRBC	0 /100 WBC			0
Absolute nRBC	k/uL			0.00
Diff Type		Auto Diff		Auto Diff
Iron	41 - 186 ug/dL		**20 (L)**	**12 (L)**
TIBC	232 - 386 ug/dL		356	372
Transferrin Saturation	15 - 57 %		**6 (L)**	**3 (L)**
Retic %	0.4 - 2.0 %			**2.2 (H)**
Abs Retic	0.0180 - 0.1000 M/uL			0.088
Ferritin	14.7 - 205.1 ng/mL		26.9	**5.5 (L)**

CBC + DIFF
Reference Range & Units: %

Normocytic Anemia

- Can be the hardest to diagnose properly
- Retics usually normal or decreased
- Most frequently needs a bone marrow to diagnose
- Other concurrent medical conditions become very important; liver, kidney, endocrine, inflammatory, malignant disease



Normocytic Anemia

Endocrine disease

- Hypothyroidism
- Hyperthyroidism
- Addison's disease
- Panhypopituitarism
- Testicular failure

Renal disease

- High creatinine
- Low, inappropriately low Epo

If No liver, renal, or endocrine disease or esp if high epo level

Needs a marrow exam

- Hypoplasia/aplastic anemia
- Leukemia/malignant infiltration
- Myelodysplastic syndromes

Mineral imbalance

- Copper deficiency
- Zinc overload

https://www.sciencedirect.com/topics/medicine-and-dentistry/normochromic-normocytic-anemia.

Thrombocytopenia

- Definition
  - Less than 150,000/ul
  - May have some slight local variance
- Pseudothrombocytopenia
  - 1:1000 to 1:10,000 specimens
  - EDTA clumping
  - Typically solved with citrate or heparinized tube
  - Found on peripheral smear exam

Thrombocytopenia and pseudothrombocytopenia. On-line. Accessed on 11/17/2020 from: https://www.sciencedirect.com/topics/medicine-and-dentistry/pseudothrombocytopenia.

History Questions Thrombocytopenia

- What medications is the patient taking? Which ones are new?
- Alcohol exposure?
- Recent transfusions?
- Are there HIV risk factors?
- Is there a family history of thrombocytopenia?

Thrombocytopenia and pseudothrombocytopenia. On-line. Accessed on 11/17/2020 from: https://www.sciencedirect.com/topics/medicine-and-dentistry/pseudothrombocytopenia.

Physical Examination

- Petechiae
  - Dependent, traumatized areas
  - Mucous membrane, epistaxis, GI bleeding
- Purpura
- > 50,000 counts rarely associated with any increase in hemorrhage
- Adenopathy, splenomegaly, hepatomegaly

Thrombocytopenia and pseudothrombocytopenia. On-line. Accessed on 11/17/2020 from: https://www.sciencedirect.com/topics/medicine-and-dentistry/pseudothrombocytopenia.

Acquired Production Problems

- Marrow infiltration
  - Replacement of normal hematopoietic elements with something else
  - Possible inhibitory effect of secondary process affecting mega function
- Treat the underlying process to improve platelet count

- Cancer, leukemia, lymphoma, multiple myeloma
- Myelofibrosis
- Osteoporosis
- Infectious processes
- Toxins, Viruses
- Drugs
- Folate/B12/iron deficiency
- Pure amegakaryocytic thrombocytopenia
- Myelodysplastic syndrome

Thrombocytopenia and pseudothrombocytopenia. On-line. Accessed on 11/17/2020 from: https://www.sciencedirect.com/topics/medicine-and-dentistry/pseudothrombocytopenia.

Drugs Are a Common Cause

- Hospital:
  - Heparin, LMWH, sulfa, valproic acid, quinine/quinidine, gold salts, penicillins, vancomycin, linezolid, cephalosporins, cocaine
  - Anti-IIb/IIIa drugs – can cause acute severe drops
- Outpatient:
  - Quinidine, quinine, rifampin, digoxin
  - Acetaminophen, Bactrim, danazol, cimetidine, chorothiazide, lithium diazepam, sulfisoxazole
  - Piperacillin, methicillin
  - Minoxidil, DES, nitroglycerin, tamoxifen
  - Zantac, Tegretol, Dilantin, Motrin, captopril, ampicillin, procainamide, HCTZ

Arnold, D. (2020). Drug induced immune thrombocytopenia. On-line. Accessed on November 17, 2020 from https://www.uptodate.com/contents/drug-induced-immune-thrombocytopenia.

What Is ITP?

- Idiopathic (or Immune) Thrombocytopenic Purpura
  - Acquired autoimmune disorder
  - Antibodies or activated T cells targeted against platelets leading to their destruction
- Two major criteria for diagnosis
  - Low platelet count (with normal WBC and RBC)
    - Otherwise normal blood smear
  - No apparent condition to blame it on
  - ***Note the lack of a definitive test***

Arnold, D. (2020). Drug induced immune thrombocytopenia. On-line. Accessed on November 17, 2020 from https://www.uptodate.com/contents/drug-induced-immune-thrombocytopenia.

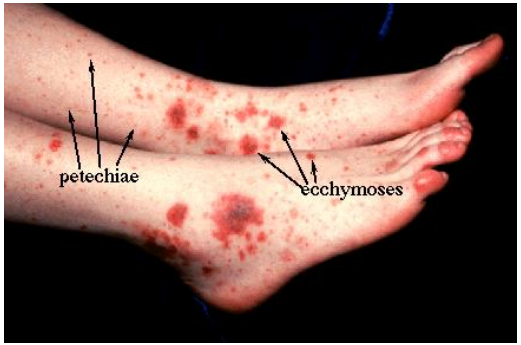
Diagnosis of ITP

- Laboratory evidence of low platelet count
  - Check HCV and HIV antibodies in adults
- Blood smear examination to rule out other diagnoses
- Careful history (especially drug/toxin exposure) and physical exam
  - Should NOT have large liver, spleen, adenopathy
- Bone marrow examination is advised if exam findings are abnormal

Arnold, D. (2020). Drug induced immune thrombocytopenia. On-line. Accessed on November 17, 2020 from https://www.uptodate.com/contents/drug-induced-immune-thrombocytopenia.

Whom to Treat in ITP?
Key: Are They Bleeding or Not

- Normal platelet count 150,000-450,000/μL
- Symptomatic patients with platelet counts < 30,000-50,000/μL
- Asymptomatic patients with counts below 10,000/μL
- Treat with: Corticosteroid taper, IVIg



Arnold D. 2020. Drug induced immune thrombocytopenia. On-line. Accessed on November 17, 2020 from https://www.uptodate.com/contents/drug-induced-immune-thrombocytopenia.

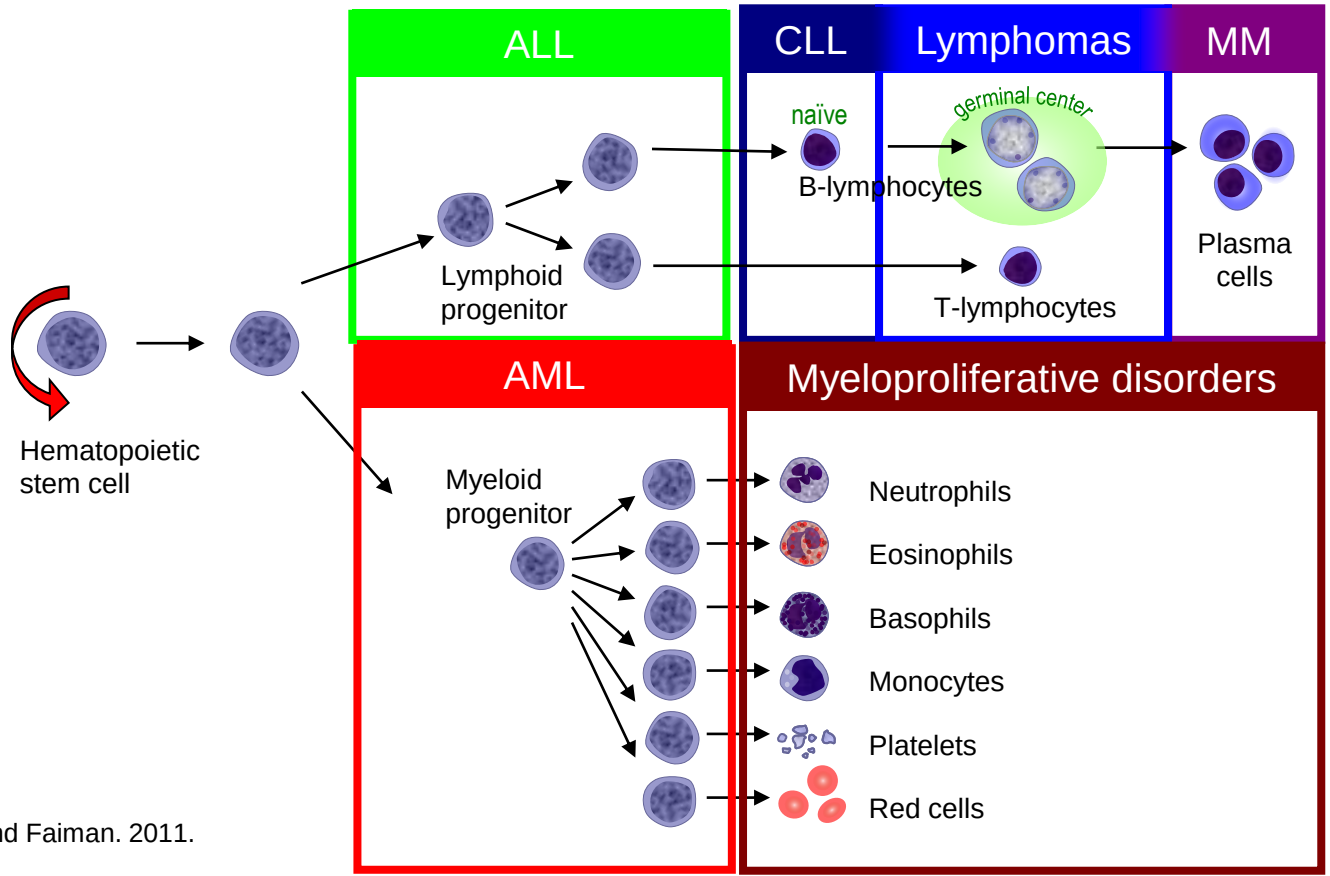
RhAPP
RHEUMATOLOGY ADVANCED PRACTICE PROVIDERS

Hematologic Cancers: An Overview

Hematologic (Blood) Cancers: Causes and Risk Factors

- Proposed associations with environmental or external factors:
  - Agent Orange, benzene, radiation
- Leukemias and lymphomas are most common in caucasians; MM African American males
- Rare familial cases in MM, CLL are not well understood
- Smoking cigarettes (acute leukemia)

Remember This Slide?



Tariman and Faiman. 2011.

Features of Common Blood Cancers

	Acute Leukemias (AML and ALL)	MDS	Chronic Leukemias (CML and CLL)	Lymphomas (Hodgkins, Non-hodgkins)	Multiple Myeloma
Definition	Increase of clonal immature "blasts" in the bone marrow which can be found in the blood	Spectrum of clonal, hematologic stem cell malignancies	Accumulation of lymphocyte clones in blood, bone marrow, and lymphoid tissue	Cancer of lymph nodes	Cancer of plasma cells
Epidemiology/Age	14,590/Y, 67y (AML) 6,070/Y, 14y (ALL); 40% will be >20yrs	15,000/Y (70y)	5,920/Y, 64y(CML) 15,680/Y, 71y (CLL)	9,290/Y, 38y (HL) 69,740 /Y, 66y (NHL)	22,300/Y, 69y
Presentation/ Hallmarks	Anemia, infection, bleeding;F, WL	Anemia, infection, bleeding	Incidental, fevers, lymph node swelling; wl ns	fevers, lymph node swelling;; f,wl , ns	Kidney disease, protein in urine, bone pain, anemia; WL
Incidence	Age related Male>Female	Age related Female>Male	Age related Male>Female	Age related Male>Female	Age related Male>Female

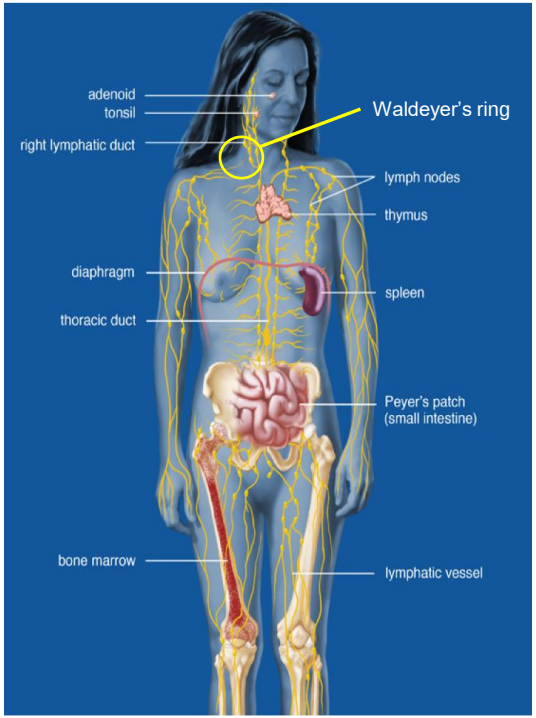
Overview of Hematologic Cancers. December 4, 2020 I 47.

F = fever; NS = night sweats; WL = weight loss.

Howlader N, Noone AM, Krapcho M, Garshell J, Neyman N, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). *SEER Cancer Statistics Review.* 1975-2010, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2010/, based on November 2012 SEER data submission, posted to the SEER web site, 2020.

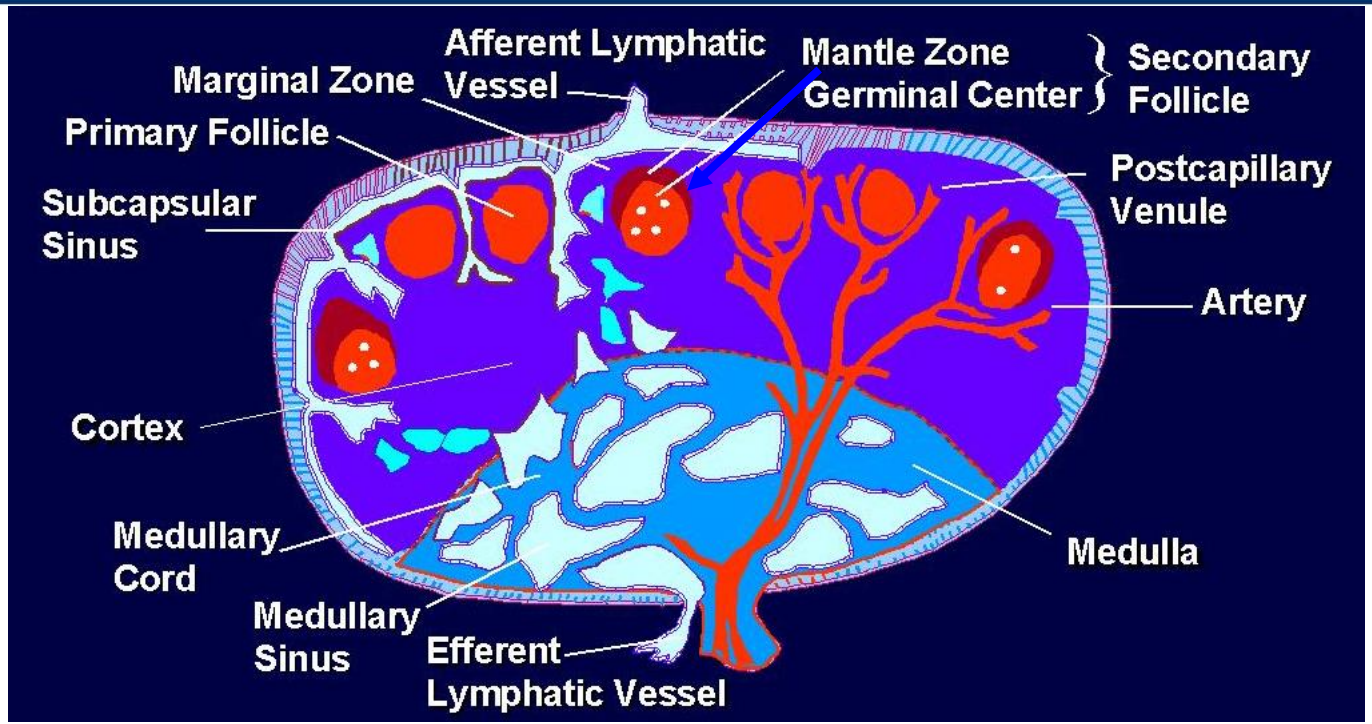
Pathways of Lymphoma

- Lymphatic vessels, nodes, and organs
- Primary organs
  - BM, thymus
- Secondary organs
  - LNs
  - Spleen
  - MALT
  - Waldeyer’s ring



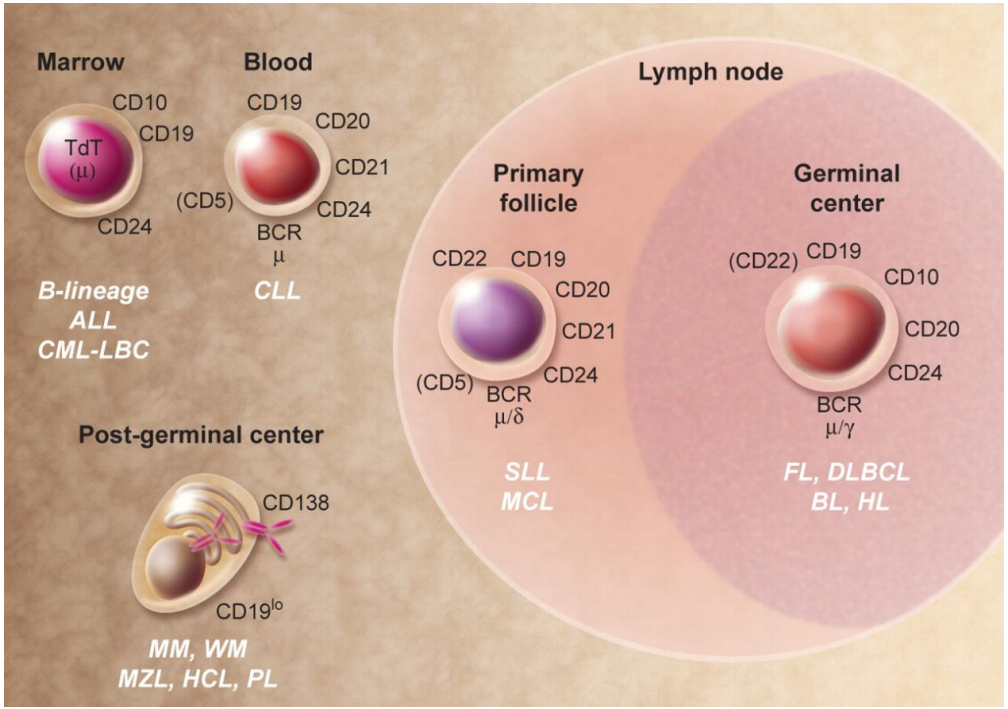
BM = bone marrow; LNs = lymph nodes; MALT = mucosa-associated lymphoid tissue.

Normal LN Organization



Overview of Hematologic Cancers. December 4, 2020 I 49.
Adapted from Willard-Mack. 2006.

Flow Cytometry: The Zip Code for Primary Cell Type of B-Cell Neoplasms



Overview of Hematologic Cancers. December 4, 2020 l 50.
CML-LBC = chronic myeloid leukemia-lymphoid blast crisis; HL = Hodgkin lymphoma.
LeBien, et al. 2008.

Types of Leukemia, Lymphoma: Indolent to Aggressive

Indolent	Aggressive	Very Aggressive
CLL/SLL	MCL	Precursor B-lymphoblastic lymphoma/leukemia
Lymphoplasmacytic/ Waldenstroms (WM)	Follicle center lymphoma, follicular, grade 3	B-cell acute leukemia
MZL	DLBCL	Therapy undertaken with curative intent
Follicle center lymphoma, follicular, grade 1/2	Primary mediastinal large B-cell lymphoma	Cure rates vary
Most are incurable	Require immediate therapy	
Goal is control and minimize symptoms	Variable treatment goals	
	Cure rates vary	

Overview of Hematologic Cancers. December 4, 2020 l 51.
WM = Waldenström's macroglobulinemia.

Diagnostic Evaluation of Blood Cancers

Diagnostic Study	Clinical Significance
CBC + differential + platelets Reticulocyte count	• Evaluate presence of cytopenias, lymphocytosis, morphological abnormalities, and BM response to anemia
LDH, haptoglobin, coombs, and reticulocyte count	• Evaluate for underlying hemolysis
LDH	• Necessary for risk stratification using IPI • Evaluate for aggressive disease, risk for TLS, and hemolysis
Serum β_2m	• Prognostic relevance • Reflects WBC membrane turnover • Levels are affected by renal function
Hepatic profile	• Treatments have potential renal and hepatic toxicities or may be affected by renal or hepatic insufficiencies • Serum albumin reflects nutritional status and used to estimate prognosis

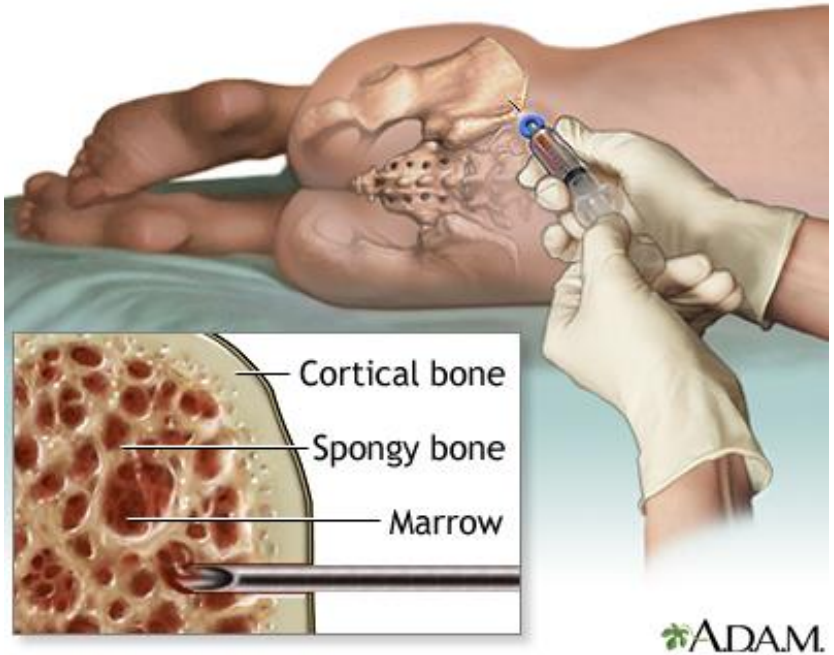
Diagnostic Evaluation of Blood Cancers

Diagnostic Study	Clinical Significance
MUGA scan or echocardiogram	• Baseline evaluation for patients receiving anthracycline therapy
CT chest, abdomen, and pelvis	• Current standard of care for initial staging on NHL • Estimation of anatomic extent of disease and areas of abnormal LNs (> 1 cm)
^{18}FDG-PET	• PET with FDG shows functional metabolic status reported as SUV • Useful in evaluation of LNs < 1 cm • Scanning after a few cycles of therapy have been shown to predict treatment outcomes in MCL
CXR	• Baseline evaluation for any underlying disease

MUGA = multi-gated acquisition scan; CT = computed tomography;
^{18}FDG-PET = 18-fluorodeoxyglucose-positron emission tomography; CXR = chest X-ray; LNs = lymph nodes;
SUV = standardized uptake value.
NCCN, 2020.

Diagnostic Evaluation of Blood Cancers

Diagnostic Study	Clinical Significance
Aspirate	Evaluation of morphological abnormalities -flow cytometry, FISH analysis, and cytogenetics
Biopsy Should be of adequate size for evaluation (1–2 cm)	Cellularity, presence of lymphocytic infiltrates, exclusion of other BM disorders
Cytogenetics, FISH	“Blueprint” for prognosis; XY or XX



Staging and Prognosis: Common Blood Cancers

	Acute Leukemias (AML and ALL)	MDS	Chronic Leukemias (CML and CLL)	Lymphomas (Follicular, Diffuse large B-cell & Hodgkins)	Multiple Myeloma
Staging System	French-American-British (FAB) or WHO classification, FAB: subtypes, M0 through M7, based on blood counts, differentiation of cells; WHO: classifies according to genetic abnormalities	FAB, WHO; IPSS-r prognosis Looks at blasts, cytopenias, cytogenetics	CLL-Rai includes 5 stages of CLL: Stage 0 , lymphocytosis only, best survival Stages III and IV are high risk with short survival (months), lymphocytosis, anemia, low plts CML “phases: CP, AP, and BP (mos)	Generally stage 1-IV; A= absence of b symptoms(night sweats, fevers, wt loss; B= presence Various prognosis systems NHL: International Prognostic Index (IPI uses APLES for prognosis (age, PS, nodal sites)	International staging system (ISS) looks at two blood tests: Serum b2m, albumin
Prognosis	90% of adults will die of acute leukemia	Higher blast count=higher risk of progression to AML	Lower stages =longer survival; years vs months	Lower stages =longer survival; years vs months	Median survival as high as 7.3 years with nl cytogenetics
Curable	In some with transplant	Generally not	Generally not with CLL; possibly with CML and new agents	In some with NHL, HD	Generally not

Overview of Hematologic Cancers. December 4, 2020 l 55.
CP = chronic phase; AP = accelerated phase; WBC = white blood cell; NCCN, 2020.

Key Takeaways

- Abnormalities in ones' blood counts are a sign of an underlying condition, which may not often be serious
- Watchful waiting is often appropriate
- Consult hematology, Primary provider if unknown cause

Key Takeaways #2

- Blood cancers arise from the bone marrow
- Although most are incurable, most are highly treatable
- Knowledge of the basics of hematology will allow for prompt and appropriate evaluation and can make a difference!

Cleveland Clinic