Diagnosing Anemias Like a Pro!

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Speaker has no relationship to disclose.

Objectives

- Understand pathophysiology of RBC production/destruction (10 mins)
- Evaluate components of CBC for preliminary diagnosis of anemia (25 mins)
- Select and interpret complementary lab studies to systematically diagnose anemias (25 mins)

Outline

- Background
- Case studies to help you figure out how to systematically diagnose anemias

Concept #1 Let's start from the beginning!

Where do RBCs come from?

a. Liver
b. Spleen
c. Kidney
d. Bone marrow

Why does the bone marrow make RBCs?

…because erythropoietin told it to!

Erythropoietin (EPO) is an endocrine hormone made in the kidney!

Liang R, Ghaffari S. Advances in understanding the mechanisms of erythropoiesis in homeostasis and disease. *Br J Haematol*. 2016 Jul 21.

When bone marrow is exposed to EPO…

RBC production can increase 5-fold!

Liang R, Ghaffari S. Advances in understanding the mechanisms of erythropoiesis in homeostasis and disease. *Br J Haematol.* 2016 Jul 21.

Concept #1

RBCs are produced by the bone marrow in response to EPO.

Reticulocytes

Erythrocyte

Reticulocytes = 1% of circulating RBCs

Spend about 3 days in the bone marrow, then are released into circulation. After the 4th day……

…reticulocyte becomes an ERYTHROCYTE!

- NO nucleus!
- Biconcave discs
- Very flexible and can change shape to get thru capillaries

Lifespan of RBCs

RBC

Born: Jan 1
Died: Apri 15

Live for about 100-120 days and then are "eaten" by macrophages and removed from circulation.

As long as…..

Rate of RBCs
Removed (1%) = Rate produced (1%)
All is good!
No anemia, no polycythemia!

"Mrs. Boudreaux"

42-year-old female, otherwise healthy, non-smoker

CC: **Fatigue for the past 4-6 weeks; attempted to donate blood and was refused related to "low blood count"**

Rule 1:

Anemia is Never Normal!

Always suspect that something is going on with your patient!

Adamson JW, Longo DL. Anemia and polycythemia. *Harrison's Principles of Internal Medicine*. 15th ed. New York, New York: McGraw-Hill; 2001. Vol 1.: 348-354.

"Mrs. Boudreaux"

42-year-old female, otherwise healthy

CC: **Fatigue for the past 4-6 weeks; attempted to donate blood and was deferred related to "low blood count"**

History: **SOB when walking up stairs, denies chest pain, *no history of recent weight loss, loss of appetite, denies fever/night sweats***

denies dark or bloody stools; reports heavy monthly menses R/T uterine fibroid

So, the anemia appears to be something of recent onset. If this had been lifelong, what might be part of your differential?

"Mrs. Boudreaux"

42-year-old female, otherwise healthy

Meds: **none (no ASA, no herbals, no OTCs)**

FH: **Adopted, does not know FH (thinking of thalassemia, hemoglobinopathy, etc.)**

PE: **Pale conjunctiva, Grade I/VI systolic murmur, no lymphadenopathy, no jaundice or hepatosplenomegaly, *denies bone pain***

Rectal exam WNL, stool: brown, heme negative

Mrs. Boudreaux' CBC
Is our patient anemic?

CBC	Patient	Normal Values
WBC	8.0	4-10 million/mm3
Hgb	8.1 g/dL	12.6-16.1 g/dL
Hct	24.3%	38-47.7 %
RBC	3.8	3.93 – 5.69 million/mm3
MCV	60	80-99.5 fL
MCH	20	27.5-33.3 pg/cell
MCHC	34.2	33.3-35.5 g/L
RDW	16.5	11.4-14.4%
Platelets	500,500	150,000-400,000x10^3 uL
Reticulocyte count	3%	0.5-1.5%
Absolute Retic count	40,000	25,000-75,000 ul

Rule 1:

Anemia is Never Normal!

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Mrs. Boudreaux' CBC

What kind of anemia?

CBC	Patient	Normal Values
WBC	8.0	4-10 million/mm3
Hgb	8.1 g/dL	12.6-16.1 g/dL
Hct	24.3%	38-47.7 %
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Peripheral Smear

"Window to the bone marrow"

Normocytic, normochromic Red Blood Cells

Microcytic, hypochromic Red Blood Cells

Mrs. Boudreaux' Blood Smear: microcytic, hypochromic red cells

Normocytic, normochromic Red Blood Cells

Microcytic, hypochromic Red Blood Cells

Normal

"Mrs. Boudreaux"

Microcytic, Hypochromic Anemia

Differential Diagnosis:

- Iron deficiency
- Thalassemia
- Anemia of chronic disease
- Sideroblastic anemia

DeLoughery TG. Microcytic anemia. *N Engl J Med*. 2014 Oct 2. 371(14):1324-31.

Mrs. Boudreaux' CBC

What does the increased RDW indicate?

CBC	Patient	Normal Values
WBC	8.0	4-10 million/mm3
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Hct	24.3%	38-47.7 %
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RDW

RDW (red cell distribution width):
indicates degree of variation in RBC size (<15% is normal)

Anisocytosis

Red cells are not the same size!

Mrs. Boudreaux' CBC

What does the increased PLT count indicate?

CBC	Patient	Normal Values
WBC	8.0	4-10 million/mm3
Hgb	8.1 g/dL	12.6-16.1 g/dL
Hct	24.3%	38-47.7 %
RBC	4.1	3.93 – 5.69 million/mm3
MCV	60	80-99.5 fL
MCH	20	27.5-33.3 pg/cell
MCHC	34.2	33.3-35.5 g/L
RDW	16.5	11.4-14.4%
Platelets	500,400 uL	150,000-400,000x10^3 uL
Reticulocyte count	3%	0.5-1.5%
Absolute Retic count	40,000	25,000-75,000 uL

Thrombocytosis? Why?

"Poor Man's Sed Rate"

- Chronic IDA
- Chronic infection
- Inflammatory disorders ("Poor man's sed rate")
- Malignancy

Kuku I, Kaya E, Yologlu S, Gokdeniz R, Baydin A. Platelet counts in adults with iron deficiency anemia. *Platelets*. 2009 Aug 3. 1-5.

What might *Thrombocytopenia* (in the presence of anemia) indicate?

- Aplastic anemia
- Hypersplenism
- Marrow involvement with malignancy
- Autoimmune platelet destruction
- Folate, B12 deficiency

Kuku I, Kaya E, Yologlu S, Gokdeniz R, Baydin A. Platelet counts in adults with iron deficiency anemia. *Platelets*. 2009 Aug 3. 1-5.

Mrs. Boudreaux' CBC

Should pancytopenia be part of diff dx?

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Mrs. Boudreaux' CBC

Is hemolysis occurring in this patient?

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WBC	8.0	4-10 million/mm3
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RDW	16.5	11.4-14.4%
Platelets	500,400	150,000-400,000x10^3 uL
Reticulocyte count (uncorrected)	3%	0.5-1.5%
Absolute Retic count	40,000	25,000-75,000 uL
LDH	220	0-300 U/L

What is Hemolysis?

Responsible for about 5% of anemias

Premature destruction of RBCs:

- Inherited disorders (Sickle cell anemia, thalassemia)
- Malaria
- Hemolytic anemia (G6PD deficiency)

Consider hemolysis if rapid fall in hemoglobin, reticulocytosis, and/or abnormally shaped RBC-spherocytes or RBC fragments-on peripheral smear

What lab tests are indicative of hemolysis?

The most sensitive measure is LDH.
Reticulocyte count may indicate hemolysis.

LDH

- Lactate dehydrogenase (lactic acid dehydrogenase)
- Enzyme that is abundant in all body tissues
- RBCs are LOADED with LDH; but only small amounts in the blood!!!

What causes rises in LDH?

- Hemolysis → RBCs are LOADED with LDH
- Tissue damage → MI
- Tumor production → Malignancies

LDH

- Criterion for hemolysis
- Highly sensitive for hemolysis
- NOT specific: LDH could be released from neoplastic cells, liver, or other damaged organs
- LDH 1 and 2 are specific for RBC destruction but also present in patients who have an MI

Hempel EV, Bollard ER. The Evidence-Based Evaluation of Iron Deficiency Anemia. *Med Clin North Am*. 2016 Sep. 100 (5):1065-75.

Normal LDH: Hemolysis unlikely. What about retics?

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Mrs. Boudreaux' CBC

Is the retic count appropriate?

CBC	Patient	Normal Values
WBC	8.0	4-10 million/mm3
Hgb	8.1 g/dL	12.6-16.1 g/dL
Hct	24.3%	38-47.7 %
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What are reticulocytes?

- Reticulocytes are immature RBCs
- Measure of bone marrow's ability to produce RBCs when they are needed

Reticulocyte counts

- Normal % of retics is about 1%
- During anemia, retic % should be at least 2% if bone marrow is functioning properly (and has the ingredients needed to make new RBCs)

What's the difference between retic count and absolute retic count?

CBC	Patient	Normal Values
WBC	8.0	4-10 million/mm3
Hgb	8.1 g/dL	12.6-16.1 g/dL
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Reticulocyte Count
in presence of anemia

- During anemic states, retic % may appear increased and not reflect the true response of the bone marrow to the anemia. It has to be corrected….

Absolute Reticulocyte Count

- This is the corrected count!!!
- Uses the patient's hematocrit to calculate (takes the anemia into account)
- It is reported as the absolute retic count

Absolute Reticulocyte Count

- This is part of initial evaluation to determine whether anemia is due to loss of RBCs or inadequate production

↑ Reticulocyte count with anemia

- ↑ RBC production
- ↑ Bleeding
- ↑ Hemolysis

Hempel EV, Bollard ER. The Evidence-Based Evaluation of Iron Deficiency Anemia. *Med Clin North Am*. 2016 Sep. 100 (5):1065-75.

↓ Reticulocyte count with anemia

Bone marrow failure

↓RBC production

Hempel EV, Bollard ER. The Evidence-Based Evaluation of Iron Deficiency Anemia. *Med Clin North Am*. 2016 Sep. 100 (5):1065-75.

So, her absolute retic count was normal….significance?

CBC	Patient	Normal Values
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Reticulocyte count	3%	0.5-1.5%
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Normal or Decreased Reticulocyte Count

- IDA, B12, folate anemia ***without supplementation***
- Chronic renal failure
- Aplastic anemia
- Lymphoma
- Post-radiation

Hempel EV, Bollard ER. The Evidence-Based Evaluation of Iron Deficiency Anemia. *Med Clin North Am*. 2016 Sep. 100 (5):1065-75.

So, if she has IDA and we supplement with iron, what *should* happen to her retic count?

a. Increase
b. Decrease
c. Stay the same

So, here's what we know…

- Microcytic, hypochromic anemia
- RDW elevated (IDA?)
- NO hemolysis
- Retic count appropriate

Microcytic, Hypochromic Anemia

Differential Diagnosis:

- ***Iron deficiency:*** micro, hypo, RDW elevated
- ***Thalassemia:*** micro, hypo, RDW normal
- ***Anemia of chronic disease:*** 80% normochromic, normocytic; 20% micro, hypo
- ***Sideroblastic anemia:*** macro or micro

*** Most common anemias are IDA, ACD**

Hempel EV, Bollard ER. The Evidence-Based Evaluation of Iron Deficiency Anemia. *Med Clin North Am*. 2016 Sep. 100 (5):1065-75.

Patient Iron Studies

Study	Patient	Normal Value
Serum Fe	30	60-152 ug/dL
TIBC	510	300-360 ug/dL
Serum Ferritin	6	40-202 ng/mL

Stools for occult blood: Negative x 3

Iron Measures: Serum Fe

Serum iron: Decreased in IDA

- Amount of iron in circulation

Iron Measures: *Don't get tricked!!!*

Serum iron: Decreased in IDA

- Should be decreased in IDA unless…… patient took iron supplement and then serum iron is measured
- Serum Fe level effected if patient takes oral Fe supplement within 24-48 hours of serum level

DeLoughery TG. Microcytic anemia. *N Engl J Med*. 2014 Oct 2. 371(14):1324-31.

Iron Measures: Serum Ferritin

Serum ferritin: Decreased in IDA

- Amount of iron in storage
- This will take 4-6 months of supplementation to replenish storage

Iron Measures: *Don't get tricked!!!*

Serum ferritin: Decreased in IDA

- Serum ferritin is an acute phase reactant, so if low, then really low
- Increased serum ferritin seen in inflammatory states, hyperthyroidism, and neoplasm

Iron Measures: Don't get tricked!!!

Serum ferritin: Take Home Point

- Normal serum ferritin does not rule out IDA

Iron Measures: TIBC

TIBC: Increased in IDA

- Total iron binding capacity is the "capacity to bind iron"

RBC Timeline

- Reticulocytosis: 3-10 days
- Increased Hemoglobin: 2-4 weeks
- Replace iron stores: 4-6 months

Causes of IDA

- *Heavy blood loss from fibroid is most likely cause!*
- Start treatment now for IDA
- Once this is corrected, anemia should resolve

Take Home Point

GI workup always mandatory if source of bleeding not identified: GI bleed, GI malignancy

Be Consistent in Approach

- Is the patient anemic?
- What kind of anemia?
- Peripheral smear OK?
- What does RDW indicate?
- What do platelets indicate?
- Is hemolysis occurring?
- What does retic count indicate?
- What else?

"Earl"

72 year old male, underweight, poor nutritional status, poor historian, VSS

CC: **Fatigue and weakness for the past 4-6 weeks; brought in to clinic by adult daughter who thinks he looks "pale and sick"**

History: **Patient consumes 8-10 EtOH drinks daily, admits to very poor dietary habits, *denies fever/night sweats, denies dark or bloody stools***

"Earl"

72 year old male, underweight, poor nutritional status, poor historian

Meds: **Inconsistently takes lisinopril for HTN**

FH: **Daughter has been estranged, patient is poor historian**

PE: **Ill-appearing, looks older than his stated age, pale conjunctiva, no lymphadenopathy, no jaundice or hepatosplenomegaly, *denies joint, bone pain,* BMI = 18; rectal exam WNL, stool: brown, heme negative**

Earl's CBC
Is our patient anemic? What Kind?

CBC	Patient	Normal Values
WBC	8.0	4-10 million/mm3
Hgb	9.1 g/dL	12.6-16.1 g/dL
Hct	27.3%	38-47.7 %
RBC	3.9	3.93 – 5.69 million/mm3
MCV	90	80-99.5 fL
MCH	30	27.5-33.3 pg/cell
MCHC	34.2	33.3-35.5 g/L
RDW	14.2	11.4-14.4%
Platelets	300,500	150,000-400,000x10^3 uL

Earl's CBC
I was expecting a macrocytic anemia

CBC	Patient	Normal Values
WBC	8.0	4-10 million/mm3
Hgb	9.1 g/dL	12.6-16.1 g/dL
Hct	27.3%	38-47.7 %
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Normocytic, Normochromic Anemia

Vast Differential Diagnosis:

- **Anemia of chronic disease (infection, inflammation, malignancy)**
- Acute blood loss
- Early IDA
- Malignancy
- Chronic renal insufficiency
- Poorly managed chronic disease
- Other less common diseases

FYI:

Chronic Diseases NOT associated with Anemia of Chronic Disease

- **COPD**
- **HF**
- **HTN**

If a patient with one of these diseases presents with anemia, look for another etiology!

Normocytic, Normochromic Anemia

Vast Differential Diagnosis:

- Anemia of chronic disease (infection, inflammation, malignancy)
- Acute blood loss
- **Early IDA**
- Malignancy
- Chronic renal insufficiency
- Poorly managed chronic disease
- Other less common diseases

FYI on Normocytic Anemias

Mild IDA can be normocytic, normochromic

MCV becomes microcytic when Hct ≤ 30

Hgb	9.1 g/dL	12.6-16.1 g/dL
Hct	27.3%	38-47.7 %
RBC	3.9	3.93 – 5.69 million/mm3
MCV	90	80-99.5 fL
MCH	30	27.5-33.3 pg/cell
MCHC	34.2	33.3-35.5 g/L
RDW	14.2	11.4-14.4%

Normocytic Anemias "Another Clue"

RDW	Causes of Normocytic Anemia
Normal	ACD, acute blood loss
Elevated	Early IDA, incompletely treated IDA, Megaloblastic anemia

Hgb	9.1 g/dL	12.6-16.1 g/dL
Hct	27.3%	38-47.7 %
RBC	3.9	3.93 – 5.69 million/mm3
MCV	90	80-99.5 fL
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Peripheral Blood Smear:

Microcytic, hypochromic RBCs

Macrocytic, normochromic RBCs

Dimorphic Smear:

2 distinct populations of red blood cells

Dx: Mixed Anemia

We need to workup BOTH!

Take Home Point

In patients who have "Mixed Anemias"

Most valuable tool is peripheral smear!!!

Microcytic Red Cells

- **Iron studies indicate IDA!!!**
- **…but what about the macrocytic cells?**

Macrocytic Anemias most common causes

- **Vitamin B12 deficiency**
- **Folic acid deficiency**

These are megaloblastic anemias.

Megaloblastic means that there is an error in DNA synthesis resulting in impaired maturation of the RBC nucleus.

Stabler SP. Clinical practice. Vitamin B12 deficiency. *N Engl J Med*. 2013 Jan 10. 368(2):149-60.

Causes of Macrocytic Anemias (not megaloblastic)

- Alcoholism
- Liver Disease
- Hypothyroidism
- Pregnancy
- Myeloma
- Others

Earl's Peripheral Blood Smear:

Microcytic, hypochromic RBCs
Macrocytic, normochromic RBCs

Macroovalocytes, hypersegmented neutrophils

What does THAT mean?

Megaloblastic vs Not

- Megaloblastic: Peripheral smear may differentiate (macroovalocytes and hypersegmented neuts)
- Non-M: Neutrophil hyperseg is usually absent
- Order B12 and folate levels, if normal, then non-megaloblastic

Stabler SP. Clinical practice. Vitamin B12 deficiency. *N Engl J Med*. 2013 Jan 10. 368(2):149-60.

Folate Deficiency

Not usually characterized by neuro changes like B12 deficiency

Decreased Intake	Malabsorption	Impaired Metabolism	Increased Needs
Alcoholics Elderly	Sprue Gastrectomy	TMP-SMX Methotrexate	Pregnancy Lactation Hyperthyroidism Others

Stabler SP. Clinical practice. Vitamin B12 deficiency. *N Engl J Med.* 2013 Jan 10. 368(2):149-60.

Serum Folate Levels

- Serum folate levels should be gotten fasting because serum folate levels can normalize after eating a meal
- Many shortcomings with serum folate levels

If you really want to know if someone…..

is folate deficient, measure a homocysteine level (elevated = deficient)

Homocysteine needs folic acid to be converted to methionine. If folic acid is not present, homocysteine levels increase.

Serum B12 Levels

Low serum B12 levels can indicate B12 deficiency, but other things can decrease B12 levels

Causes of B12 Level Decreases
Vitamin B12 deficiency
Folic acid deficiency (33% of patients)
Pregnancy
Multiple Myeloma
HIV
Others

B12 Deficiency

Characterized by neuro changes

Decreased Intake	Malabsorption	Impaired Metabolism	Increased Needs
Alcoholics Strict vegetarians	Sprue Ileitis Diverticulosis	TMP-SMX Methotrexate	Pregnancy Lactation Post Gastrectomy Cancer Hyperthyroidism

Other: Colchicine

Serum B12 Levels

Normal or elevated serum B12 levels don't RULE OUT B12 deficiency

Causes of False Normal B12 Levels
Lymphomas
Liver Disease
IDA
Hemoglobinopathy

The Workup

- Are neuro symptoms/changes present?
- Check serum Folate and B12 levels
- If normal or low normal, then homocysteine and MMA levels

The Workup

MMA	Homocysteine	Diagnosis
Normal	Normal	Unlikely B12 or Folate deficiency
Normal	Elevated	Likely Folate deficiency
Elevated	Elevated	B12 deficiency, maybe Folate deficiency

Folate Deficiency: Homocysteine increased
B12 Deficiency: Homocysteine and MMA levels increased

Earl's labs

Vitamin B12	Folate
Normal	Normal

MMA	Homocysteine
Elevated	Elevated

What's your diagnosis?

"John"

34-year-old male in his usual state of health until about 4-6 weeks ago

CC: **Fatigue for the past 4-6 weeks**

History: **SOB when walking up stairs, denies chest pain, denies dark or bloody stools but liquid stools 2-3 times daily for several weeks**

Meds: **multivitamin (no ASA, no herbals, no OTCs)**

FH: **Mother has lupus, male cousin with RA and Sjogren's syndrome**

PE: **Pale conjunctiva, sclera slightly yellow, no apparent hepatosplenomegaly**

John's Labs

CBC	Patient	Normal Values
WBC	8.0	4-10 million/mm3
Hgb	7.1 g/dL	12.6-16.1 g/dL
Hct	21.3%	38-47.7 %
RBC	2.9	3.93 – 5.69 million/mm3
MCV	105	80-99.5 fL
MCH	30	27.5-33.3 pg/cell
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RDW	14.5	11.4-14.4%
Platelets	500,400	150,000-400,000x10^3 uL

What do we know from lab analysis?

- **Patient is anemic**
- **Macrocytic, normochromic anemia, *elevated platelets***
- **RDW is a little elevated**
- **What about the peripheral smear?**

Thrombocytosis? Why?

"Poor Man's Sed Rate"

- **Chronic IDA**
- **Chronic infection**
- **Inflammatory disorders ("Poor man's sed rate")**
- **Malignancy**

John's Labs

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RDW

RDW (red cell distribution width): indicates degree of variation in RBC size (<15% is normal)

RDW	14.5	11.4-14.4%

John's labs

Vitamin B12	Folate
Normal	Normal

MMA	Homocysteine
Normal	Normal

John's Labs

CBC	Patient	Normal Values
WBC	8.0	4-10 million/mm3
Hgb	7.1 g/dL	12.6-16.1 g/dL
Hct	21.3%	38-47.7 %
RBC	2.9	3.93 – 5.69 million/mm3
MCV	105	80-99.5 fL
MCH	30	27.5-33.3 pg/cell
MCHC	34.2	33.3-35.5 g/L
RDW	14.5	11.4-14.4%
Platelets	500,400	150,000-400,000x10^3 uL

What do we know from lab analysis?

- Patient is anemic
- Macrocytic, normochromic anemia, elevated platelets
- RDW is a little elevated
- What about the peripheral smear?

John's (Preliminary) Peripheral Blood Smear:

Macrocytic, normochromic RBCs

Neutrophils: WNL (so, it's non-megaloblastic)

Nucleated red blood cells

What does THAT mean?

2 things

First: It's a Macrocytic Anemia (It's non-megaloblastic)

Non-Megaloblastic Initial Differential:

- Alcoholism
- Liver Disease
- Hypothyroidism
- Pregnancy
- Myeloma
- Others

Second: Nucleated RBCs

- Peripheral smear: demonstrates nucleated red blood cells
- This indicates marrow "stress"
- Red cell has extruded its nucleus after maturation

John's Labs

CBC	Patient	Normal Values
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RDW	14.5	11.4-14.4%
Platelets	500,400	150,000-400,000x10^3 uL
LDH	800	0-300 U/L

LDH is elevated! What does that mean?

Elevated LDH

- Patient is having hemolysis of RBCs
- 5% of anemias are hemolytic

What *else* indicates hemolysis?

Serum haptoglobin: **low levels indicate moderate to severe hemolysis**

- **Haptoglobin is an acute phase reactant; so if inflammation is present, levels can be normal or elevated in the presence of hemolysis**

Wallach, J. B. (2005). *Interpretation of diagnostic tests*. (8 ed., p. 422). Philadelphia, PA: Lippincott Williams & Wilkins.:

What *else* indicates hemolysis?

Elevated Indirect bilirubin

- **Indirect bilirubin = unconjugated**
- **Direct bilirubin = conjugated**

- ***Elevated Direct* = hepatobiliary disease**
- ***Elevated Indirect* = ??? Hepatobiliary disease**

Wallach, J. B. (2005). *Interpretation of diagnostic tests*. (8 ed., p. 422). Philadelphia, PA: Lippincott Williams & Wilkins.:

What *else* indicates hemolysis?

Elevated Indirect bilirubin

- **Usually < 3 mg/dL in hemolysis**
- **>3 mg/dL found in compromised hepatic function or cholelithiasis**

Wallach, J. B. (2005). *Interpretation of diagnostic tests*. (8 ed., p. 422). Philadelphia, PA: Lippincott Williams & Wilkins.:

John's Labs

Test	Patient	Normals
Total Bilirubin	5.0	0.2-1.2 mg/dL
Direct bili	0.2	0.0-0.3 mg/dL
AST	20	5-40 u/L
ALT	22	4-40 u/L
Alk Phos	7	30-115 u/L
TSH	2.2	0.5-4.5uU/mL
HIV	Negative	Negative

- *Elevated Direct* = hepatobiliary disease
- *Elevated Indirect* = ??? Hepatobiliary disease

So, here's what we know:

Patient DOES NOT have:

- *Liver disease:* liver disease can cause macrocytosis but normal LFTs excludes liver disease
- *Non-Megaloblastic disease*: B12 and folate levels are normal
- *HIV:* Infections can cause hemolytic anemia, but there is no evidence of infection; normal WBC

John's (Final) Peripheral Blood Smear:

Macrocytic, normochromic RBCs
Nucleated red blood cells
Neutrophils: WNL

Spherocytes present

Spherocytes

What are they and what's the significance?

- **Small, dense RBCs**
- **RBC loses it biconcave shape**
- **Autoimmune hemolytic anemia (AIHA)**

Wallach, J. B. (2005). *Interpretation of diagnostic tests*. (8 ed., p. 422). Philadelphia, PA: Lippincott Williams & Wilkins.:

What labs help confirm AIHA?

Autoimmune hemolysis typically has positive direct Coombs test.

Direct Coombs test: **If this is autoimmune hemolytic anemia, direct Coombs could evaluate presence of either IgG or C3 (complement) on *red cell surface*.**

Indirect Coombs test: **looks for antibodies in the *plasma*.**

Jager U, Lechner K. Autoimmune hemolytic anemia. Hoffman R, Benz EJ Jr, Silberstein LE, Heslop H, Weitz J, Anastasi J, eds. *Hematology: Basic Principles and Practice*. 6th ed. New York, NY: Churchill Livingstone; 2013. 614-17.

John's Lab

Test	Patient	Normal
Direct Coombs	Positive!	Negative
Indirect Coombs	Negative	Negative

Autoimmune hemolysis typically has positive direct Coombs test.

Wallach, J. B. (2005). *Interpretation of diagnostic tests*. (8 ed., p. 422). Philadelphia, PA: Lippincott Williams & Wilkins.:

What is the likely cause of this anemia?

Patient has Autoimmune Hemolytic Anemia (AIHA):

- Coombs positive hemolytic anemia
- The evidence that supports this is jaundice, elevated indirect bili, elevated LDH, positive direct Coombs (IgG)
- Peripheral smear indicates spherocytes common in warm antibody hemolytic anemia

Jager U, Lechner K. Autoimmune hemolytic anemia. Hoffman R, Benz EJ Jr, Silberstein LE, Heslop H, Weitz J, Anastasi J, eds. *Hematology: Basic Principles and Practice*. 6th ed. New York, NY: Churchill Livingstone; 2013. 614-17.

Summary and Take Home

Be Consistent in Approach

- Is the patient anemic?
- What kind of anemia?
- Peripheral smear OK?
- What does RDW indicate?
- What do platelets indicate?
- Is hemolysis occurring?
- What does retic count indicate?
- What else?

Take Home Point

Don't forget the peripheral smear!!!

Thank you!

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