Approach To Anemia

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Definition

- A reduction in one or more of the major RBC measurements
- A low hemoglobin concentration and/or low hematocrit are the parameters most widely used to diagnose anemia.

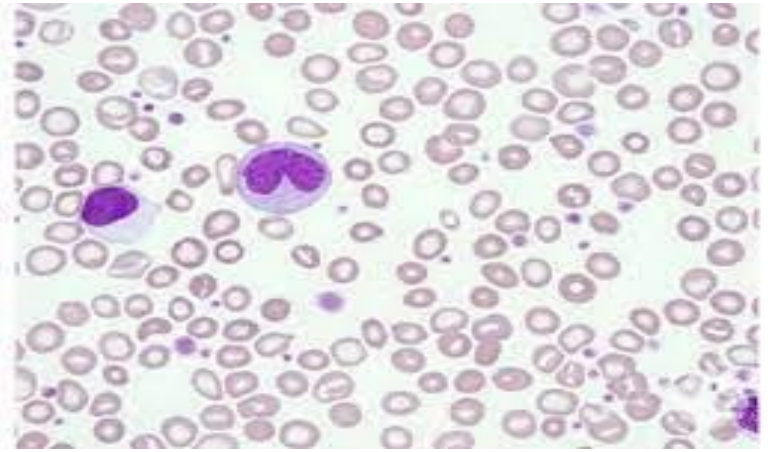
Hemoglobin

- Females: Hemoglobin 14 (+-2) g/dL
- Males: Hemoglobin 16 (+-2) g/dL
- Pregnanancy: 11 g/dL

MCV

- MCV: Mean corpuscular volume (MCV) is the average volume (size) of the RBCs

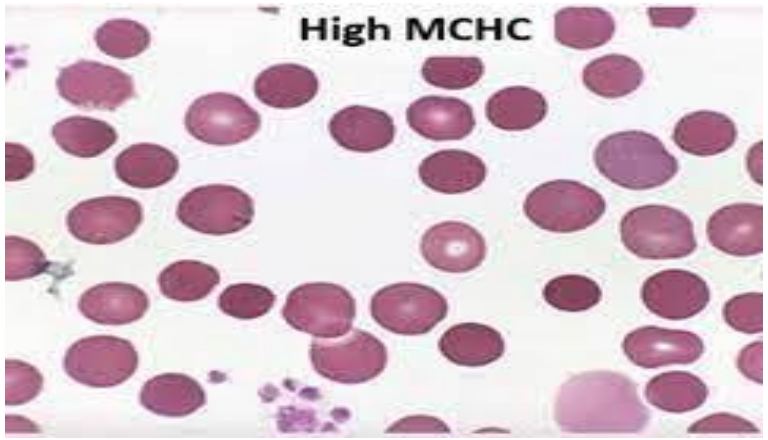
  Normal Range: 80 – 100 fl

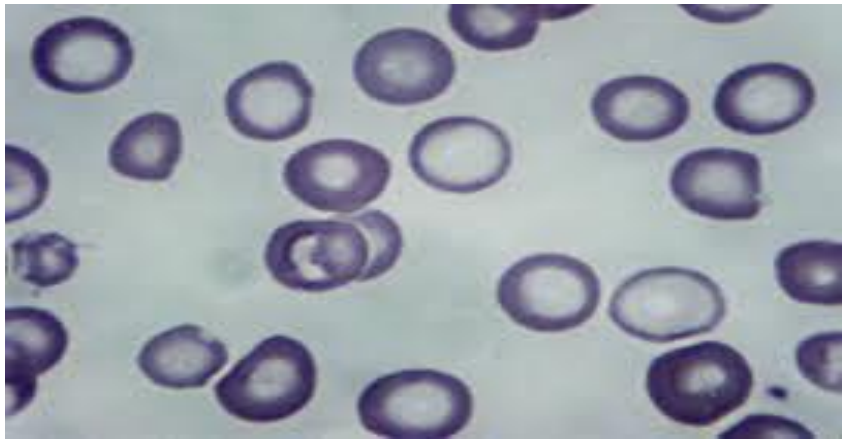


MCH

- MCH: Mean corpuscular hemoglobin (MCH) is the average hemoglobin content in a RBC.

Normal Range: 28 – 32 pg

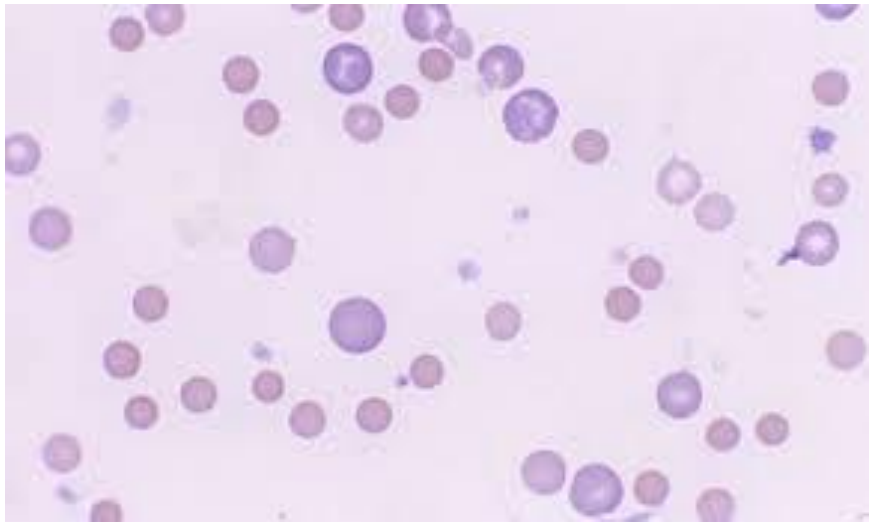


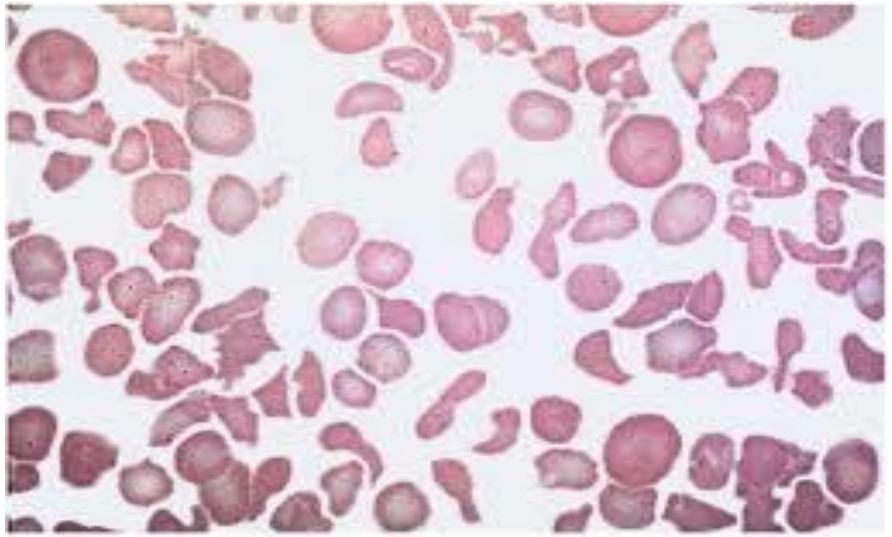


Anisocytosis Poikylocytosis

- RDW: Red cell distribution width is a measure of the variation in RBC size, which is reflected in the degree of anisocytosis on the peripheral blood smear

  Normal Range: 11.5 – 14.5 %

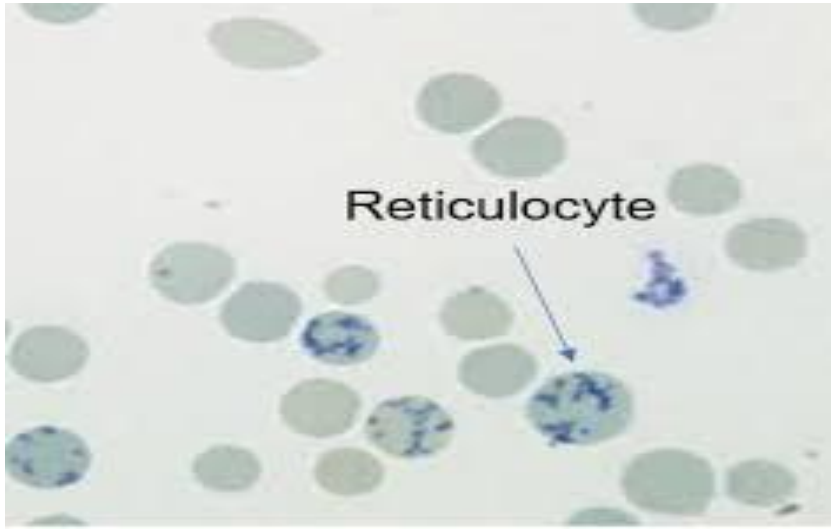


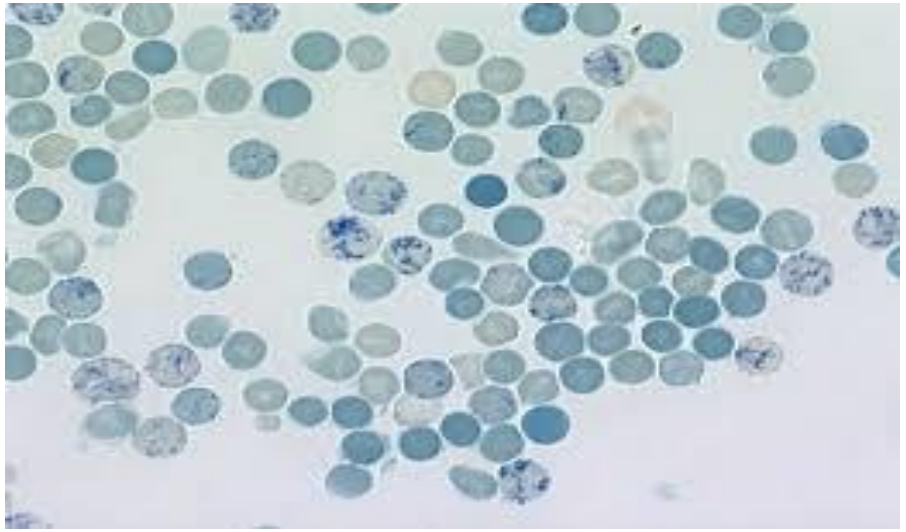


Reticulocyte

- The reticulocyte is a stage in RBC development directly before the mature RBC. The reticulocyte count reflects the rate of RBC production.

  Normal Range: 1 – 2 %, 25-100,000 microl





Normal RBC Measurment

- RBC: 4 – 5 Million
- Hb: Female: 12 – 16 Male: 14 – 18
- MCV: 80 – 100
- MCH: 28 – 32
- RDW: 11.5 – 14.5

General clinical information

A history and physical examination may identify features that increase the likelihood of specific diagnoses:

- Known underlying medical conditions and medications
- Family history of a specific type of anemia such as sickle cell disease or thalassemia
- Dietary practices (eg, vegan diet lacks vitamin B12)
- Travel (eg, acquired parasitic infections)
- Infections

General clinical information

- Bleeding (heavy menses, melena)
- Symptoms or conditions that would suggest hemolysis
- Anemia with certain food or drug exposures (fava beans, oxidant drugs)
- Symptoms or findings that suggest kidney or liver disease or hypersplenism
- Chronicity of the anemia
- Rapidity with which symptoms developed (if present)

Laboratory Tests

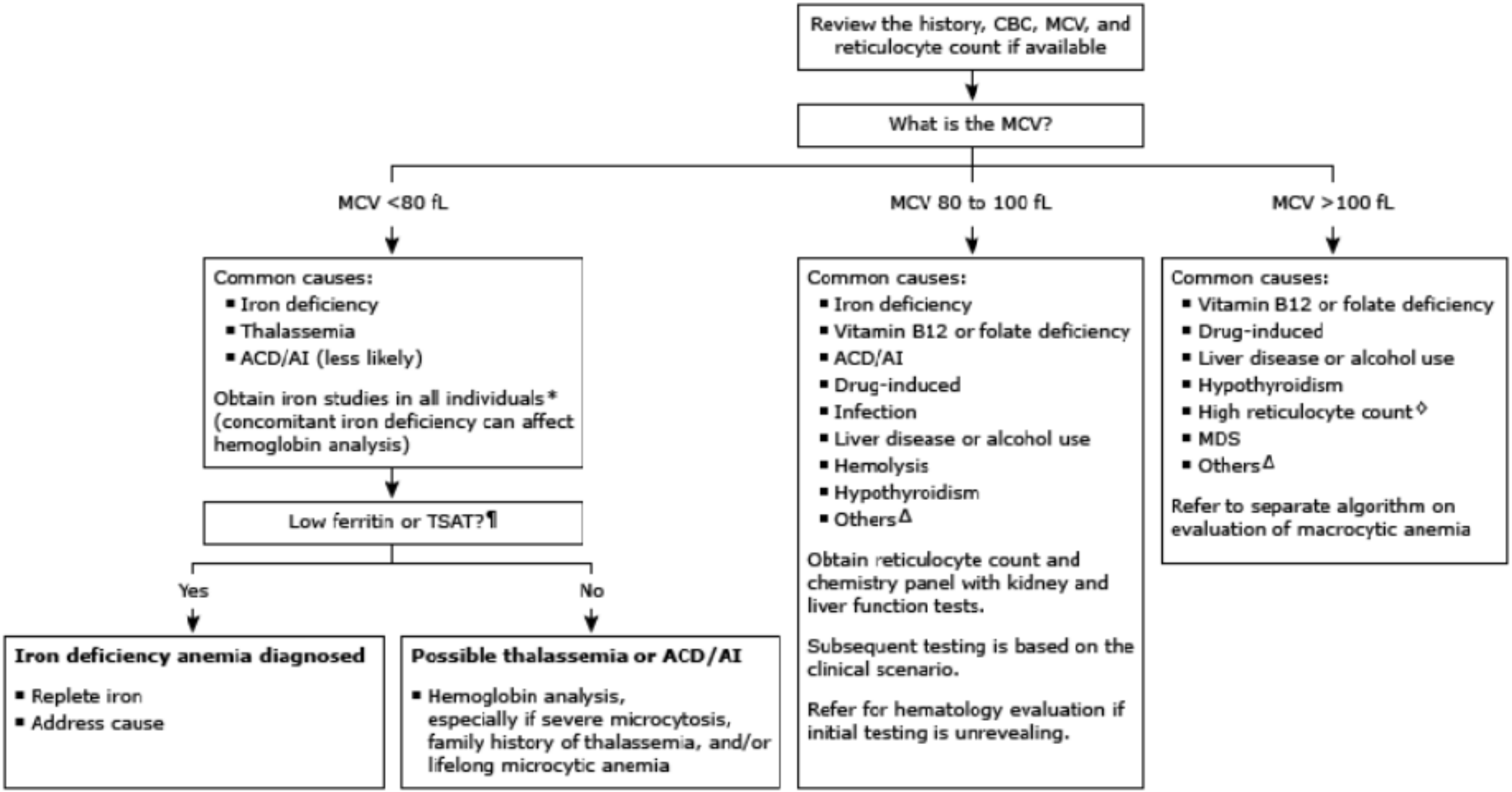
- CBC
- Reticulocyte count
- Chemistry panel: kidney and liver function tests
- Blood smear
- Hemolysis labs: LDH, bilirubin, haptoglobin, Coombs
- More extensive initial testing needed in critically ill patients
- Certain tests may be omitted in an individual with a specific diagnosis.

Case Study

- A 39-year-old woman was referred to our institution for evaluation of anemia. She was known to have multiple comorbidities. The patient denied any history of menorrhagia, any change in the appearance or color of her urine and had no history of jaundice.. Physical examination was unremarkable except for mild generalized pallor. CBC revealed the following:

  WBC:7600 **Hb:10.3** PLT:237000 RBC: 4200 **MCV: 77** RDW: 13

  The next step?


Review the history, CBC, MCV, and reticulocyte count if available
What is the MCV?
MCV <80 fL
MCV 80 to 100 fL
MCV >100 fL
Common causes:
Iron deficiency
Thalassemia
ACD/AI (less likely)
Obtain iron studies in all individuals* (concomitant iron deficiency can affect hemoglobin analysis)
Low ferritin or TSAT?¶
Yes
No
Iron deficiency anemia diagnosed
Replete iron
Address cause
Possible thalassemia or ACD/AI
Hemoglobin analysis, especially if severe microcytosis, family history of thalassemia, and/or lifelong microcytic anemia
Common causes:
Iron deficiency
Vitamin B12 or folate deficiency
ACD/AI
Drug-induced
Infection
Liver disease or alcohol use
Hemolysis
Hypothyroidism
Others Δ
Obtain reticulocyte count and chemistry panel with kidney and liver function tests.
Subsequent testing is based on the clinical scenario.
Refer for hematology evaluation if initial testing is unrevealing.
Common causes:
Vitamin B12 or folate deficiency
Drug-induced
Liver disease or alcohol use
Hypothyroidism
High reticulocyte count ◊
MDS
Others Δ
Refer to separate algorithm on evaluation of macrocytic anemia

Microcytosis (Low MCV)

- **Iron deficiency**
- **Chronic disease/anemia of inflammation**
- **Thalassemia**
- Congenital sideroblastic anemias
- Lead poisoning

Evaluation

All patients with microcytic anemia should have:

- Serum iron
- TIBC/transferrin
- Serum ferritin concentrations
- Transferrin saturation (TSAT).

Case Study

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  WBC:7600 **Hb:10.3** PLT:237000 RBC: 4200 **MCV: 77** RDW: 13

  Serum Iron: 15 Ferritin: 215 TIBC: 290

Chronic Disease Anemia

Tests	Iron Deficiency	Inflammation	Thalassemia	Sideroblastic Anemia
Smear	Micro/hypo	Normal micro/ hypo	Micro/hypo with targeting	Variable
SI	<30	<50	Normal to high	Normal to high
TIBC	>360	<300	Normal	Normal
Percent saturation	<10	10–20	30–80	30–80
Ferritin (µg/L)	<15	30–200	50–300	50–300
Hemoglobin pattern on electrophoresis	Normal	Normal	Abnormal with β thalassemia; can be normal with α thalassemia	Normal

Abbreviations: SI, serum iron; TIBC, total iron-binding capacity.

Case Study

- 43 year old male patient presenting with easy fatigue and breathlessness. On examination: Pallor

- WBC 4800 **RBC 2.8X106/µl**
- **Hb 7.4gm/dl**
- Hct 21%
- **MCV 70 fl**
- **MCH 20.8pg**
- MCHC 24.6gm/dl
- **RDW-CV 18.2%**
- **Platelets 510X106/µl**

Serum Iron: 20

Ferritin: 15

TIBC: 390

Iron Deficiency Anemia

GI Consult

Case Study

29 year old lady presented with mild pallor

- WBC 6.1X103/µl
- **RBC 5.6X106/µl**
- **Hb 10.9gm/dl**
- Hct 31.3%
- **MCV 55.8fl MCH 18.5pg**
- **RDW-CV 11.9%**
- Platelets 244X106/µl

Thalassemia Vs IDA

Thalassemia Vs IDA

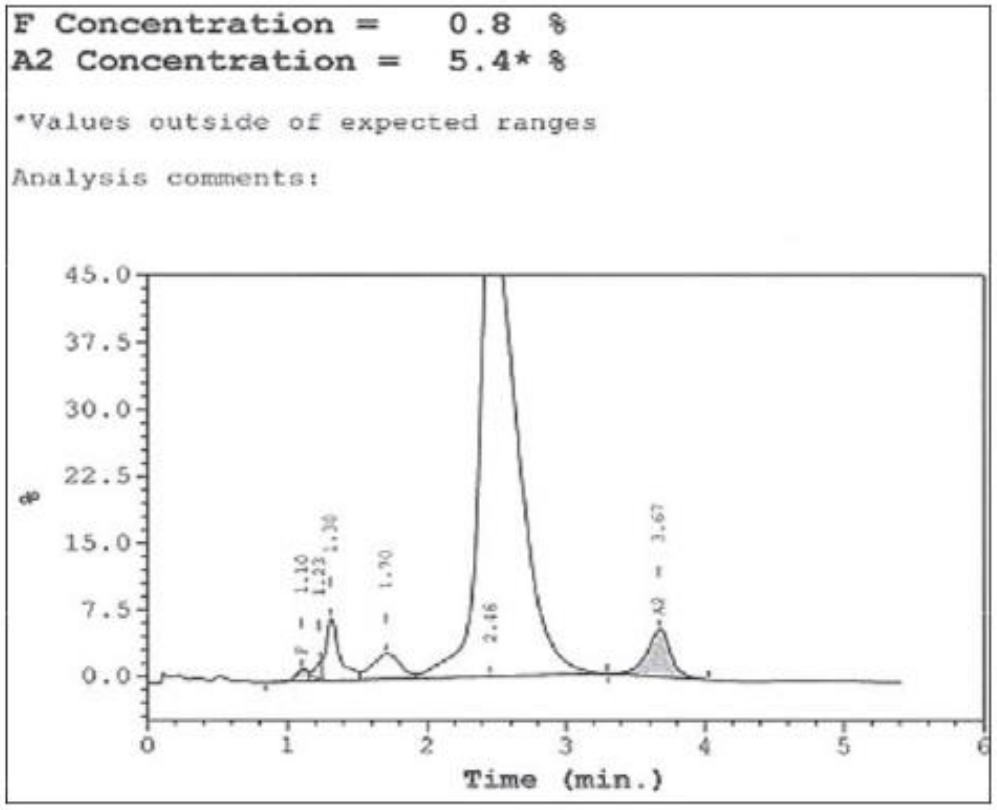
- High RBC Count
- Low RDW
- Very low MCV
- Mentzer Index: MCV/RBC Calculated :

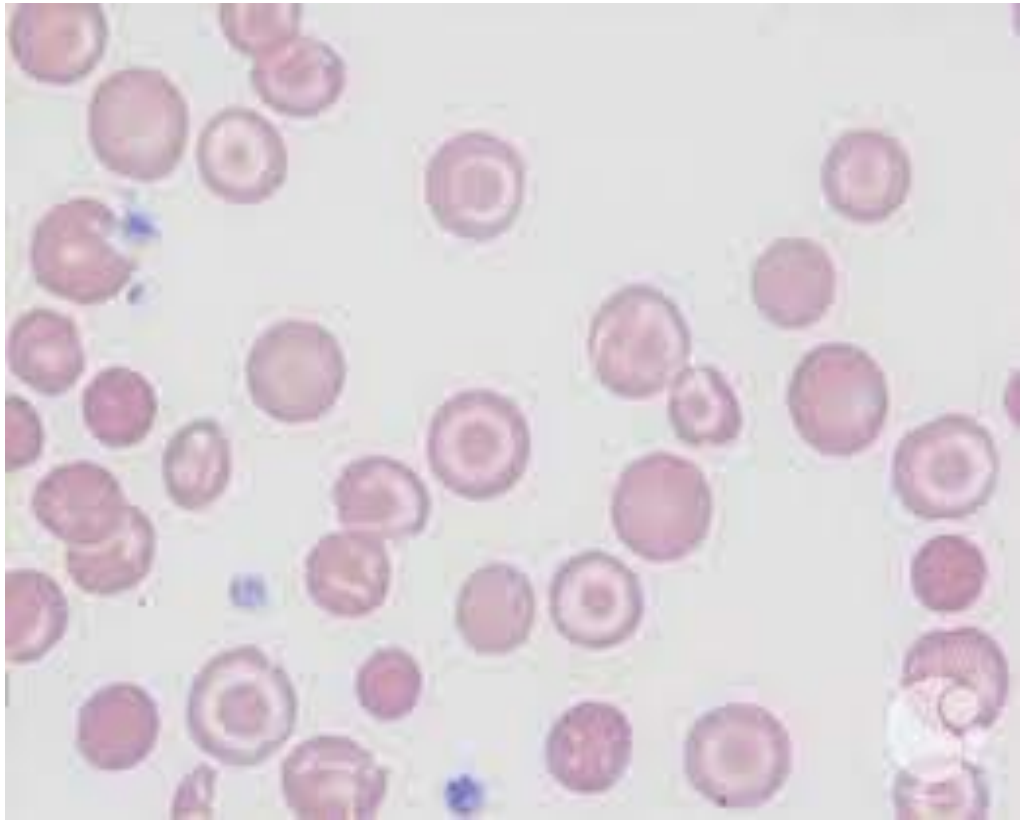
<13 – signifies thalassemia trait

>13 – signifies iron deficiency anaemia

Minor Beta Thalassemia

- Iron Profile: Normal



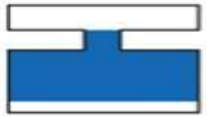


Case Study

- 18 year old female patient presenting with menorrhagia, anxiety and fatigue.

- WBC 4.8X103/µ
- RBC 4.1X106/µ
- Hb 12.1 gm/dl
- Hct 36%
- MCV 84 fl
- MCH 30.8pg
- RDW-CV 13
- Platelets 219X106/µl
- Serum Iron: 90

Iron Deficiency Anemia

	Normal	Negative iron balance	Iron-deficient erythropoiesis	Iron-deficiency anemia
Iron stores Erythron iron				
Marrow iron stores	1-3+	0-1+	0	0
Serum ferritin (µg/L)	50-200	<20	<15	<15
TIBC (µg/dL)	300-360	>360	>380	>400
SI (µg/dL)	50-150	NL	<50	<30
Saturation (%)	30-50	NL	<20	<10
Marrow sideroblasts (%)	40-60	NL	<10	<10
RBC protoporphyrin (µg/dL)	30-50	NL	>100	>200
RBC morphology	NL	NL	NL	Microcytic/ hypochromic

Case Study

A 29 Old man reffered for marriage consult:

• WBC 4.8	WBC: 5000
• **RBC 4500**	**RBC: 5300**
• Hb 15 gm/dl	**Hb 10.5 gm/dl**
• Hct 45%	Hct 30%
• MCV 78fl	**MCV 67 fl**
• MCH 30.8pg	MCH 27 pg
• RDW 13	**RDW 11**
• Platelets 219000	Platelets 390000

Iron Profile and HB electrophoresis for both is normal

WBC: 5000

RBC: 5300

Hb 10.5 gm/dl

Hct 30%

MCV 67 fl

MCH 27 pg

RDW 11

Platelets 390000

Iron profile: Normal

Hb electrophoresis: Normal

Alpha Thal trait

αα/--

α-/α-

Case Study

A 29 Old man reffered for marriage consult:

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- RBC 4500
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- Hct 45%
- MCV 78fl
- MCH 30.8pg
- RDW 13
- Platelets 219000

αα/α-

Child

- WBC: 5000
- RBC: 5300
- Hb 10.5 gm/dl
- Hct 30%
- MCV 67 fl
- MCH 27 pg
- RDW 11
- Platelets 390000

α-/--

αα/--

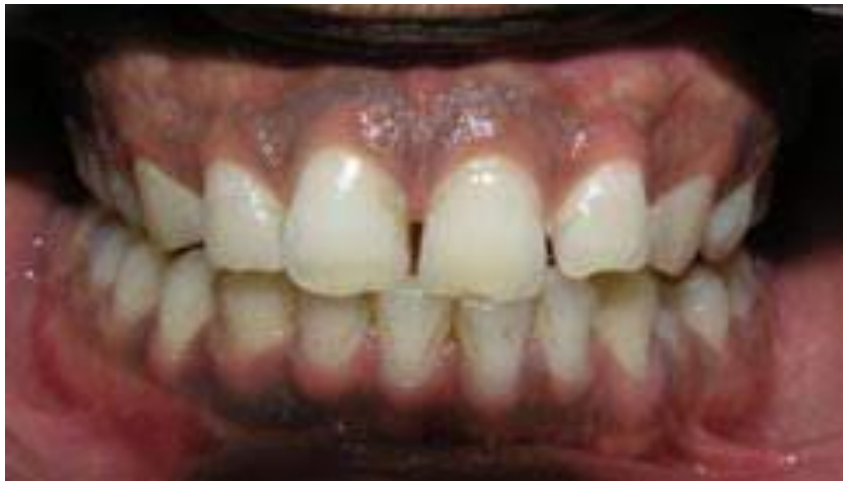
Alpha Thalassemia

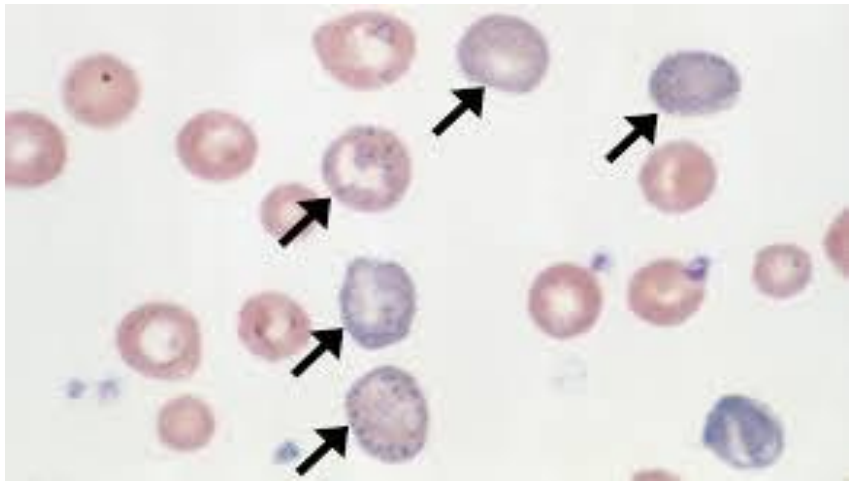
Alpha thalassemias (reduction in alpha globin chains)

Alpha thalassemia major (ATM)	(– – / – –)	Severe microcytic anemia with hydrops fetalis; usually fatal in utero	Hb Barts (γ globin tetramers); Hb Portland (embryonic hemoglobin); no Hb F, Hb A, or Hb A_2
Hb H disease	(α – / – –) or ($\alpha\ \alpha^t$ / – –)*	Moderate microcytic anemia	Hb H (up to 30%); Hb A_2 (up to 4%)
Alpha thalassemia minor (also called alpha thalassemia trait)	(α – / α –) or ($\alpha\ \alpha$ / – –)	Mild microcytic anemia	Hb Barts (3 to 8%, only in the newborn period)
Alpha thalassemia minima (also called silent carrier)	($\alpha\ \alpha$ / α –)	Normal or mildly decreased hemoglobin, normal or mildly decreased MCV	Normal

Lead Poisoning

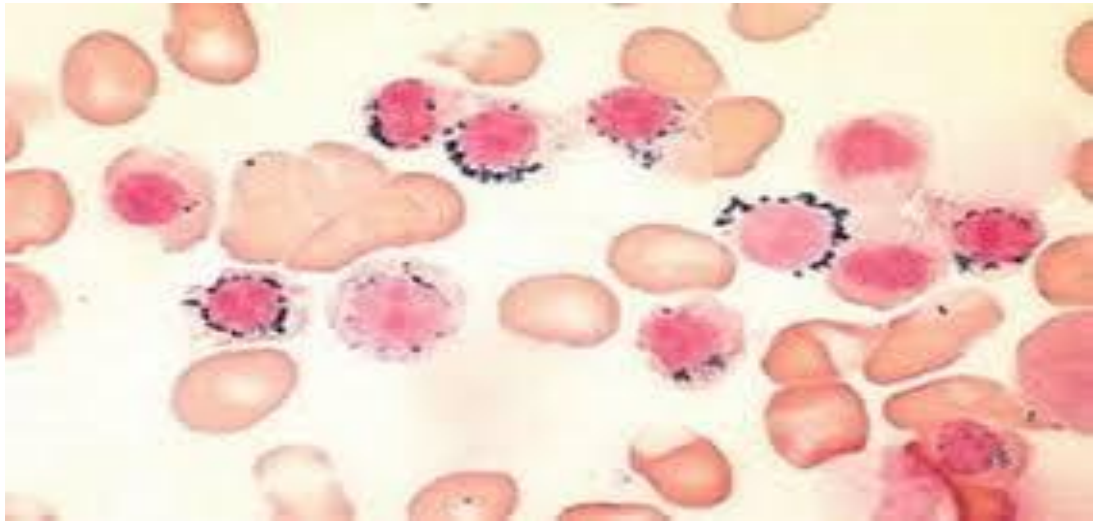
- Hypochromic Microcytic Anemia
- Abdominal pain, neurologic symptoms
- Exposure to lead paint or lead dust
- Basophilic strippling on PBS
- Removal from exposure and chelation therapy

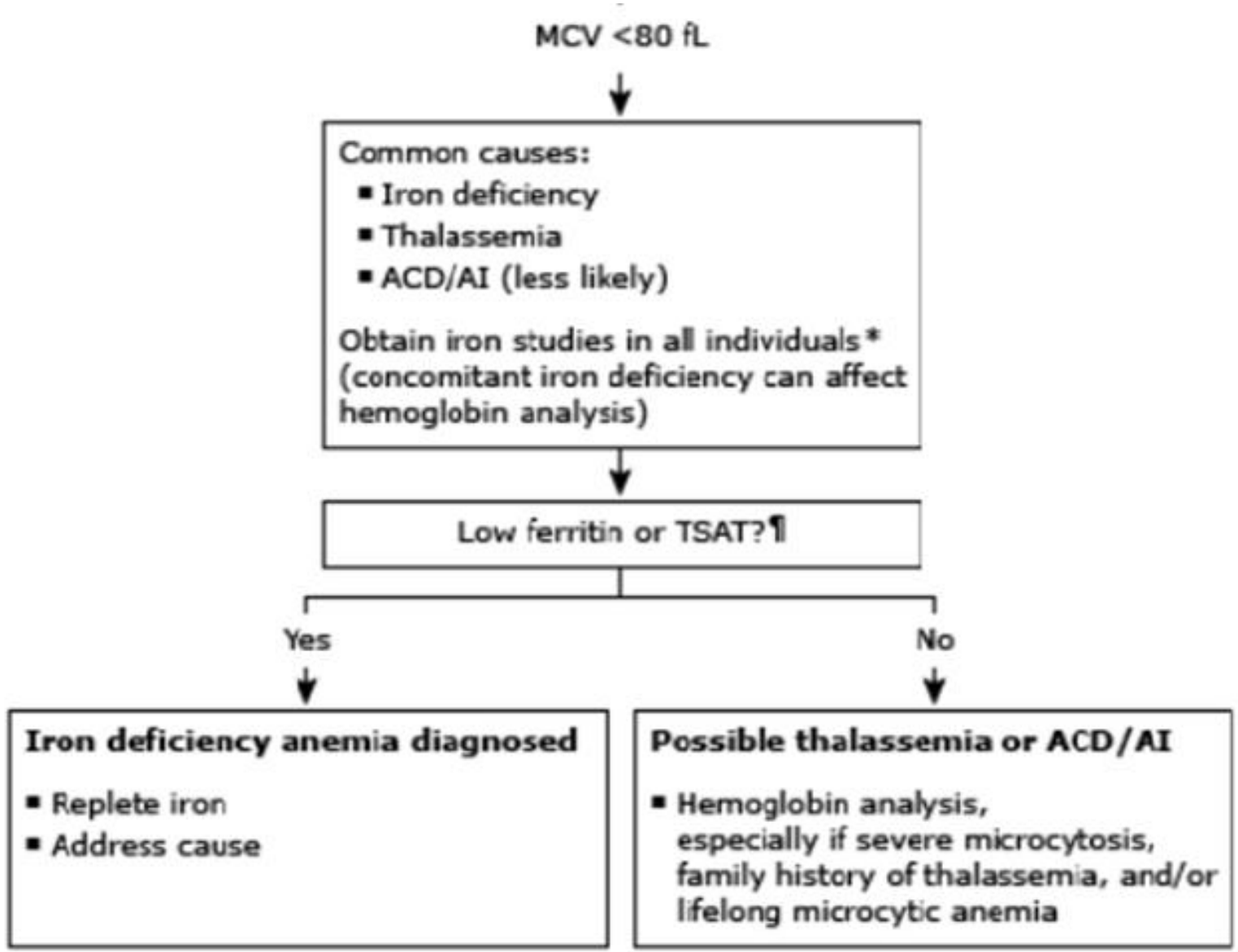




Sideroblastic Anemia

- Inherited and acquired
- Unexplained anemia after rule out of other causes
- Results from abnormal utilization of iron during erythropoiesis
- Normal to high iron levels

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Iron deficiency
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ACD/AI (less likely)
Obtain iron studies in all individuals*
(concomitant iron deficiency can affect hemoglobin analysis)
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Yes
No
Iron deficiency anemia diagnosed
Replete iron
Address cause
Possible thalassemia or ACD/AI
Hemoglobin analysis, especially if severe microcytosis, family history of thalassemia, and/or lifelong microcytic anemia

Macrocytosis (High MCV)

An increased MCV (>100 fL)

Typically attributed to asynchronous maturation of nuclear chromatin.

- Folate and cobalamin deficiency
- Liver disease
- Hypothyroidism
- Alcohol use
- MDS
- Drugs: Hydroxyurea

Evaluation

- Serum vitamin B12 level should be measured:
  All patients with unevaluated macrocytosis.
  All individuals who are nutritionally compromised
  All who have had gastric surgery

- Folate Level

- Thyroid stimulating hormone (TSH)

- Alcohol use should be assessed. The MCV typically is not >105 fL

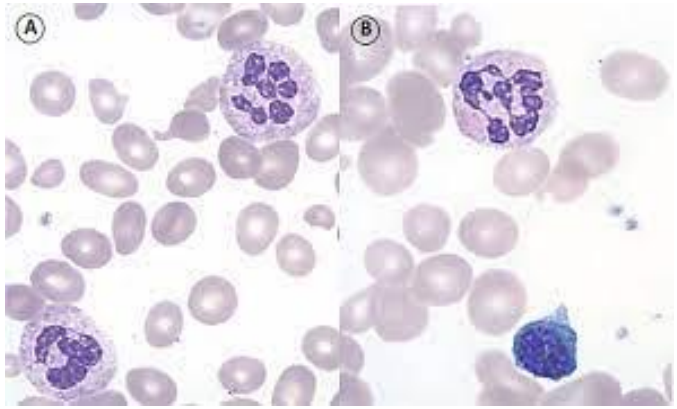
Evaluation

- The peripheral blood smear should be reviewed
- Target cells, liver synthetic tests should be measured.
- If the blood smear shows evidence of dysplasia such as bilobed or immature neutrophils or binucleate RBCs, or other cytopenias, refer to a hematologist for **bone marrow and/or molecular (DNA) studies on bone marrow**

Case Study

75 year old female presented with weight loss
On examination: Pallor, yellowish discolouration of sclera

- **WBC 2.7 X103/µl**
- RBC 1.61X106/µl
- **Hb 5.0gm/dl Hct 18.6%**
- **MCV 120fl**
- MCH 34.4pg
- **RDW-CV 19%**
- **Platelets 56X106/µl**
- **LDH: 3400**



Refractory Anemia (MDS)

- Clinically, anemia is refractory to hematinic therapy
- Dyplasia of the erythroid series only.
- Myeloblasts < 1% blood and < 5% marrow
- <15% ringed sideroblasts in marrow
- Other etiologies of erythroid abnormalities must be excluded.
- Peripheral Smear : Anisopoikilocytosis
- Dyserythropoeisis and megaloblastoid Change on Bone Marrow Aspirate

Macrocytic Anemia

- Folate and cobalamin deficiency
- Liver disease
- Hypothyroidism
- Alcohol use
- MDS
- Drugs: Hydroxyurea

Normocytic Anemia

- Anemia of chronic disease/anemia of inflammation (ACD/AI).
- Cancer-associated anemia
- Hemolytic anemia
- MDS
- Early blood loss
- Partially treated anemia
- Multiple causes: Combined microcytic plus macrocytic anemia

Evaluation

- All individuals with normocytic anemia of unknown cause should:
- chemistry panel during the initial evaluation
- Reticulocyte count Iron studies
- Hemolysis labs
- Consider conditions listed including cancer, endocrine disorders, blood loss, and nutrient deficiencies.
- **Bone marrow aspiration and Biopsy if unexplained anemia**

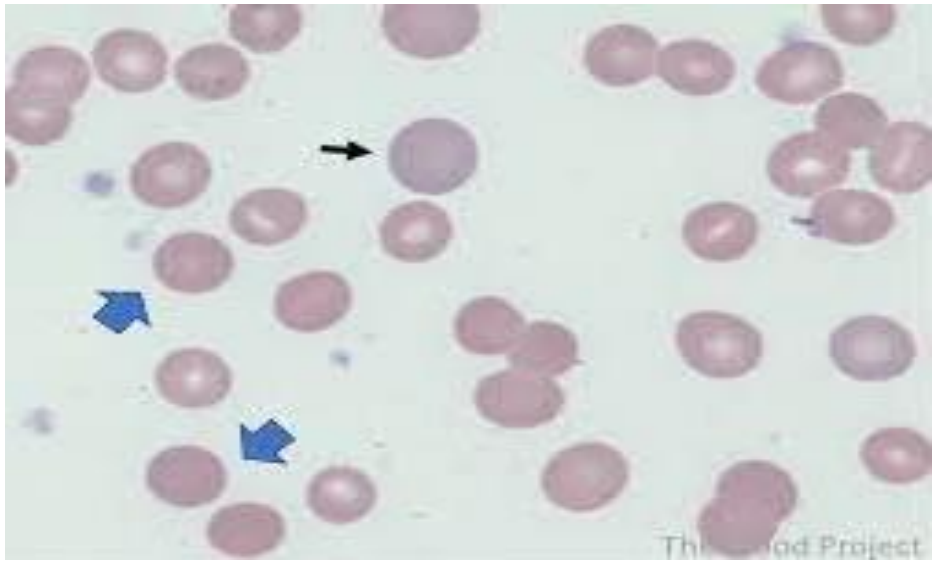
Case Study

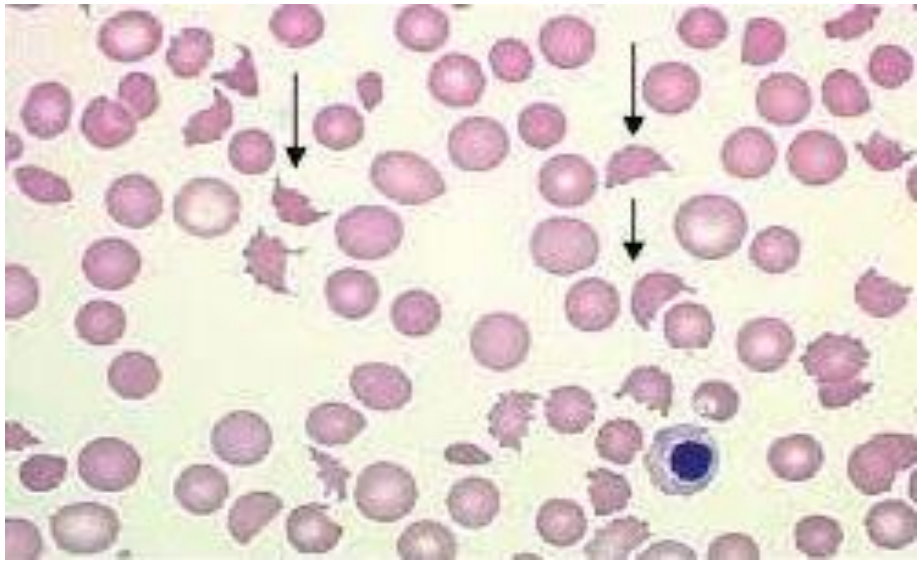
A 20-year-old female was referred with complaints of **icterus**, **dark urine** and dyspnea.

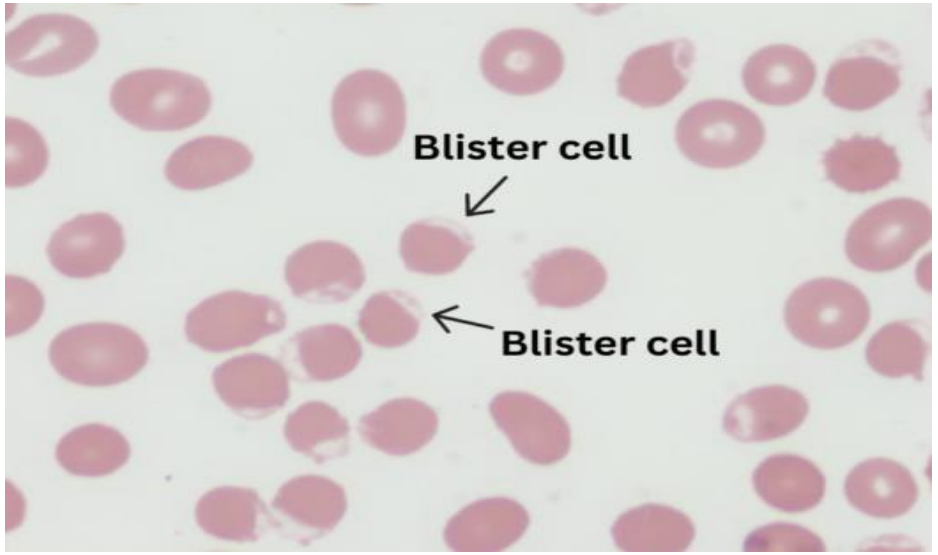
On general physical examination, there was marked **pallor**, icterus, tachycardia and tachypnea. She had mild **hepatosplenomegaly**

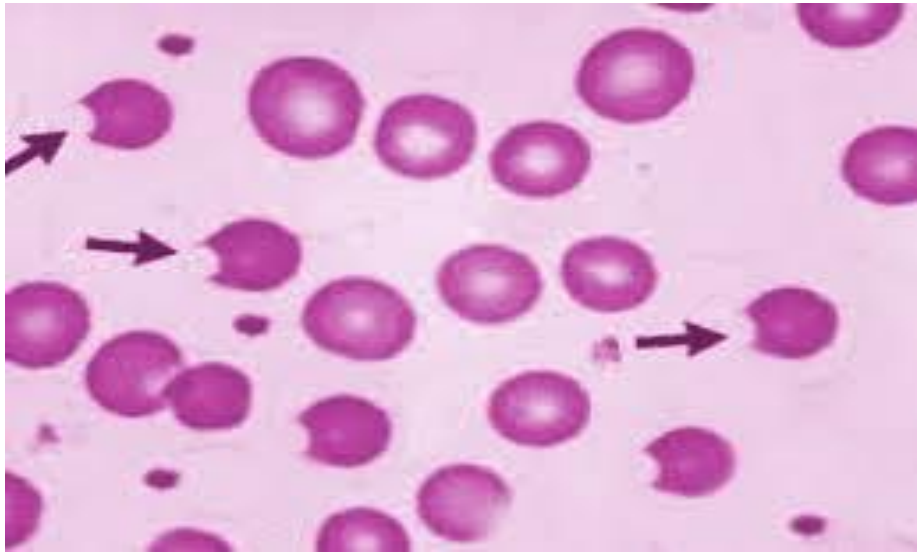
Next step?

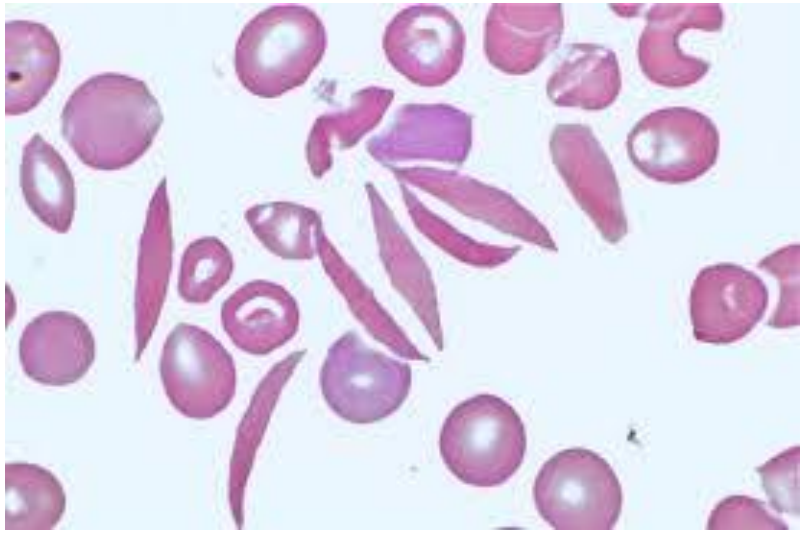
Finding	Change in hemolytic anemia
Anemia*	Decreased hemoglobin Decreased hematocrit
Bone marrow response/recovery	Increased reticulocyte count Underestimation of HbA1C
Release of RBC contents	Increased LDH Increased indirect bilirubin Decreased haptoglobin Hemoglobinemia in intravascular hemolysis ¶ Hemoglobinuria in intravascular hemolysis ¶
RBC morphology changes Δ	Spherocytes or microspherocytes in immune hemolysis Schistocytes in microangiopathic hemolysis Blister or bite cells in oxidant injury Sickle cells in sickle cell disease Target cells and teardrop cells in thalassemia

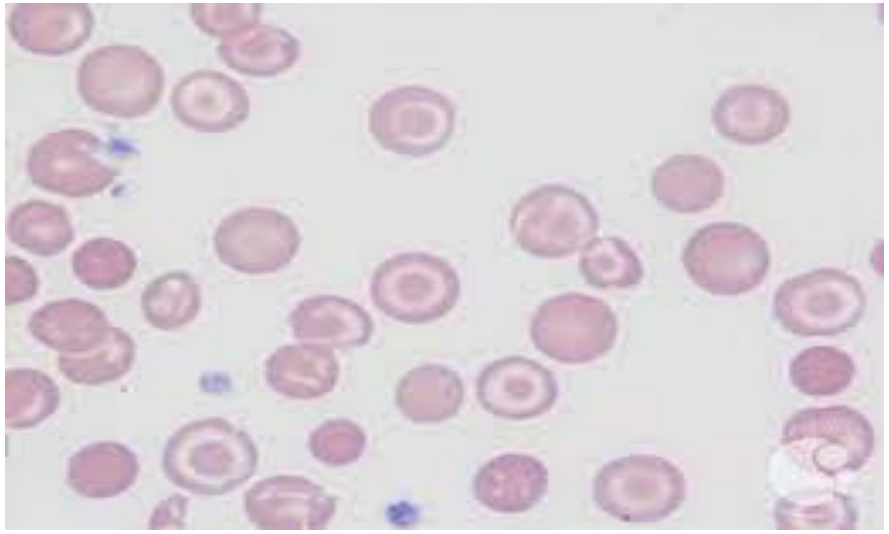


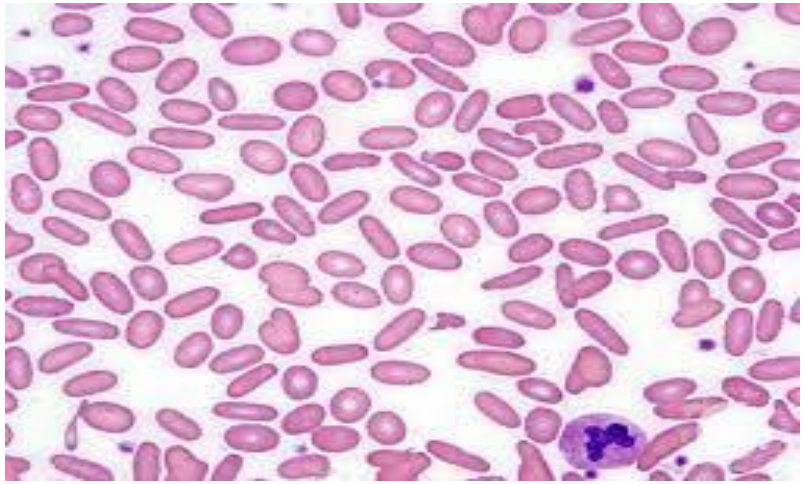


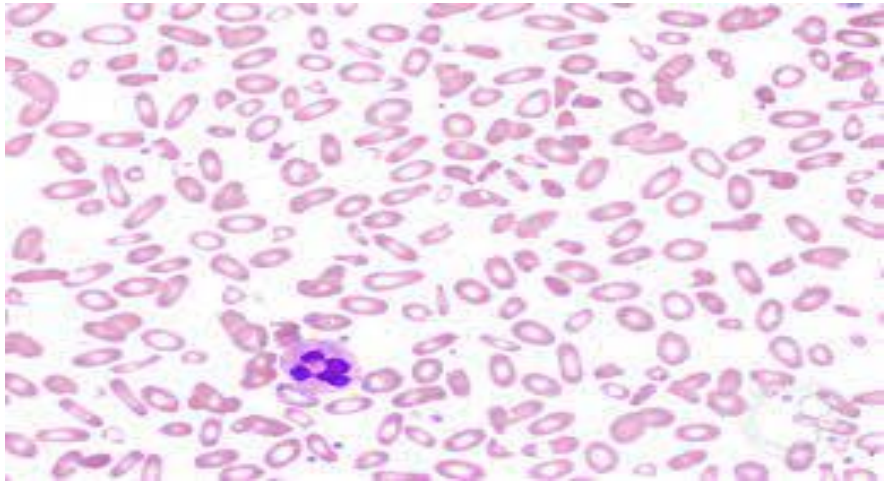

Blister cell
Blister cell

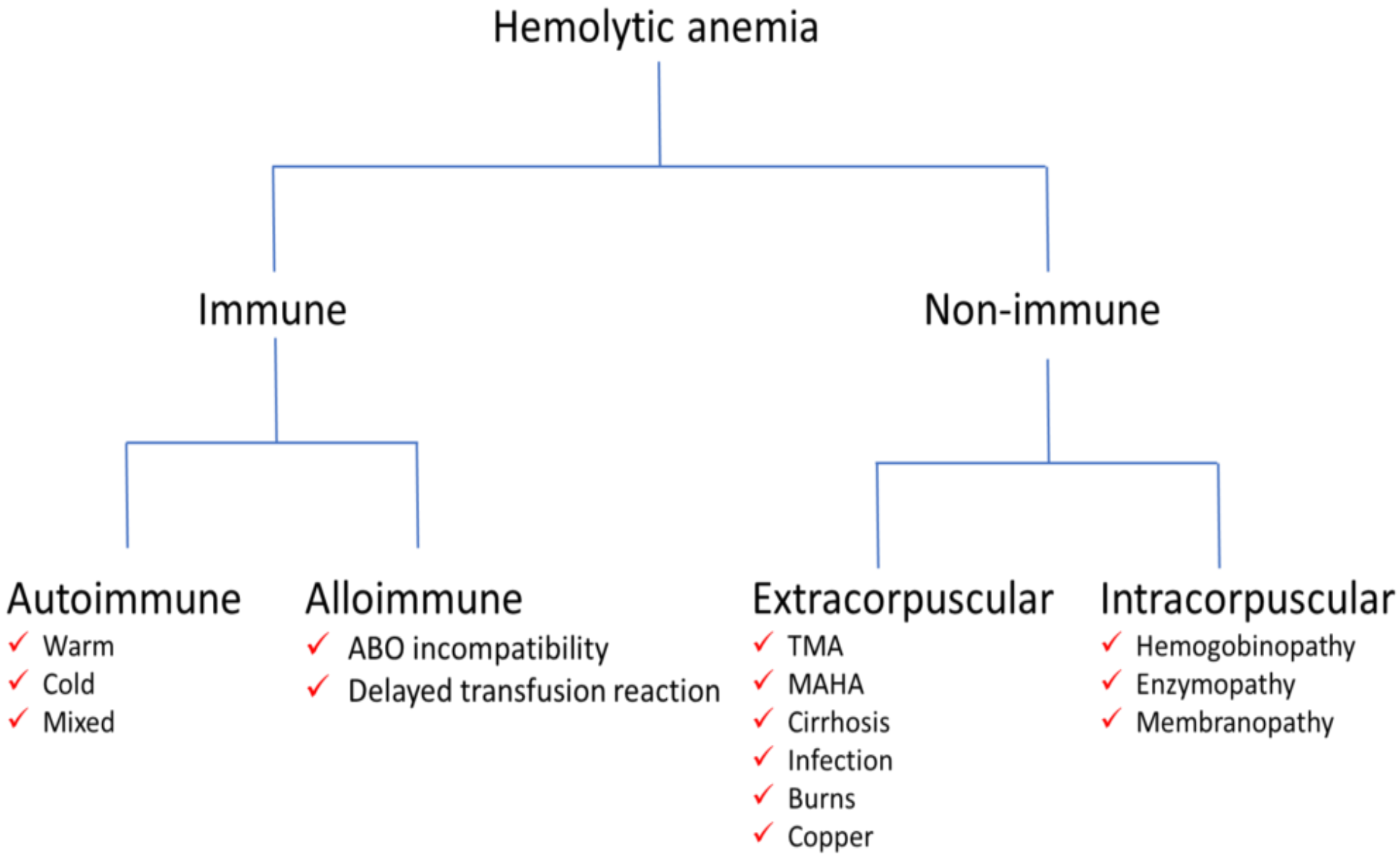




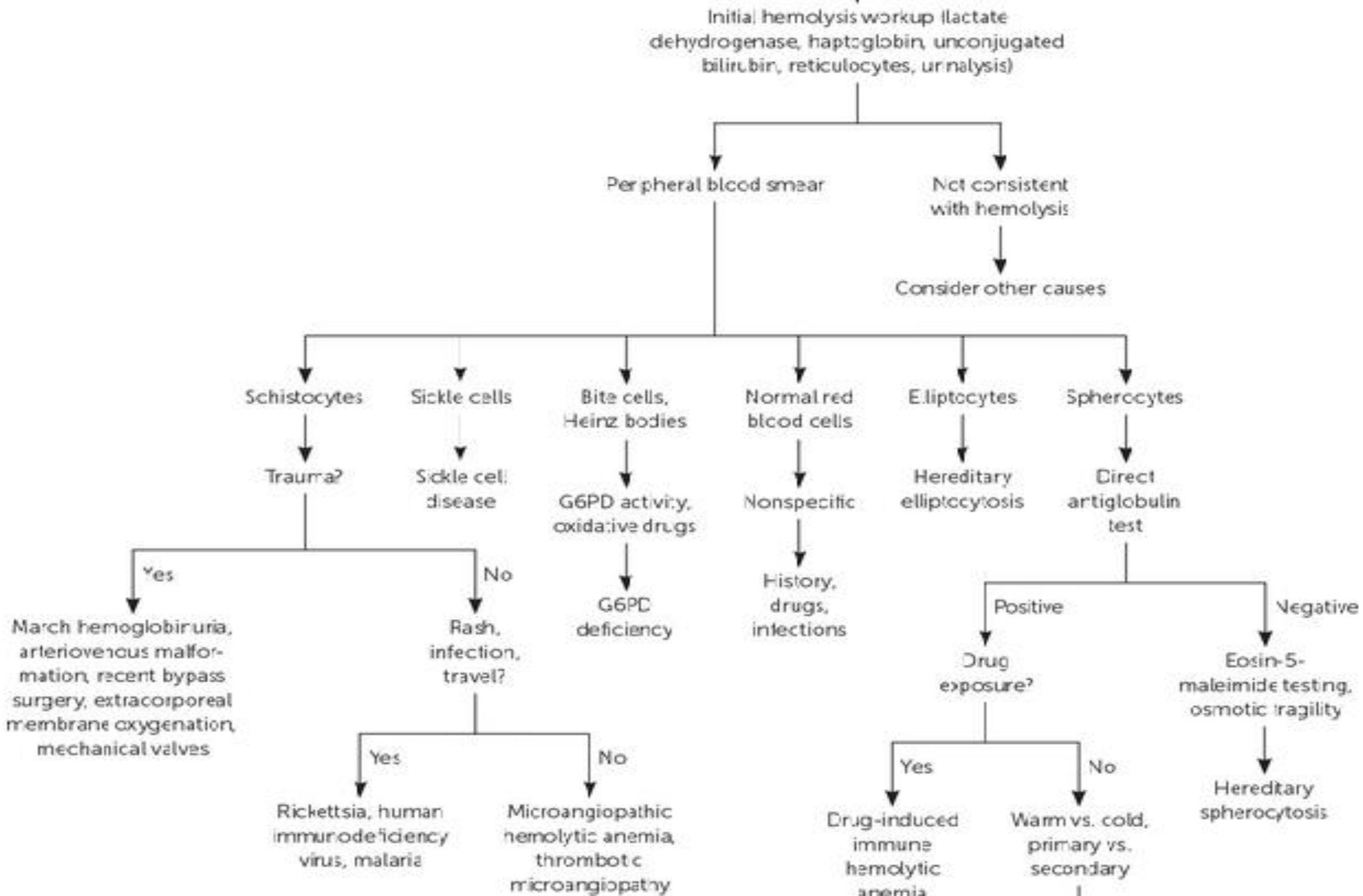







Hemolytic anemia
Immune
Non-immune
Autoimmune
✓ Warm
✓ Cold
✓ Mixed
Alloimmune
✓ ABO incompatibility
✓ Delayed transfusion reaction
Extracorpuscular
✓ TMA
✓ MAHA
✓ Cirrhosis
✓ Infection
✓ Burns
✓ Copper
Intracorpuscular
✓ Hemogobinopathy
✓ Enzymopathy
✓ Membranopathy

	Intravascular	Extravascular
Bilirubin	↑	↑↑↑
Haptoglobin	Absent	↓
Hemoglobinuria	Positive	Negative
Hemosiderinuria	Positive	Negative
Reticulocytes	↑	↑
LDH	↑	↑
Free Hemoglobin	↑↑↑	↑
Splenomegaly	Absent	Present
Iron recycling	Minimal	Maximum


Initial hemolysis workup (lactate dehydrogenase, haptoglobin, unconjugated bilirubin, reticulocytes, urinalysis)
Peripheral blood smear
Not consistent with hemolysis
Consider other causes
Schistocytes
Sickle cells
Bite cells, Heinz bodies
Normal red blood cells
Elliptocytes
Spherocytes
Trauma?
Sickle cell disease
G6PD activity, oxidative drugs
Nonspecific
Hereditary elliptocytosis
Direct antiglobulin test
Yes
No
March hemoglobinuria, arteriovenous malformation, recent bypass surgery, extracorporeal membrane oxygenation, mechanical valves
Rash, infection, travel?
G6PD deficiency
History, drugs, infections
Positive
Negative
Drug exposure?
Eosin-5-maleimide testing, osmotic fragility
Yes
No
Rickettsia, human immunodeficiency virus, malaria
Microangiopathic hemolytic anemia, thrombotic microangiopathy
Drug-induced immune hemolytic anemia
Warm vs. cold, primary vs. secondary
Hereditary spherocytosis

Finally

Bone marrow aspiration and Biopsy if unexplained anemia

THANKS FOR YOUR ATTENTION