A Practical Approach to Anemia

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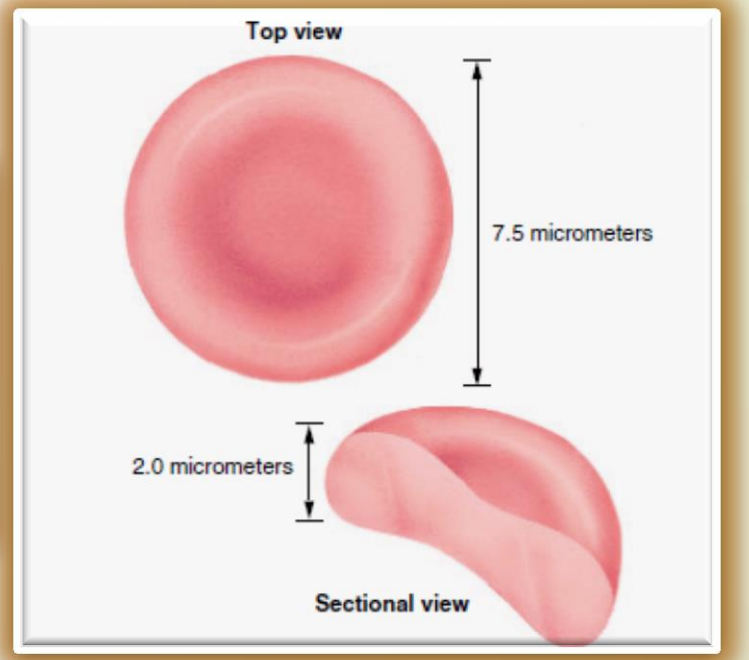
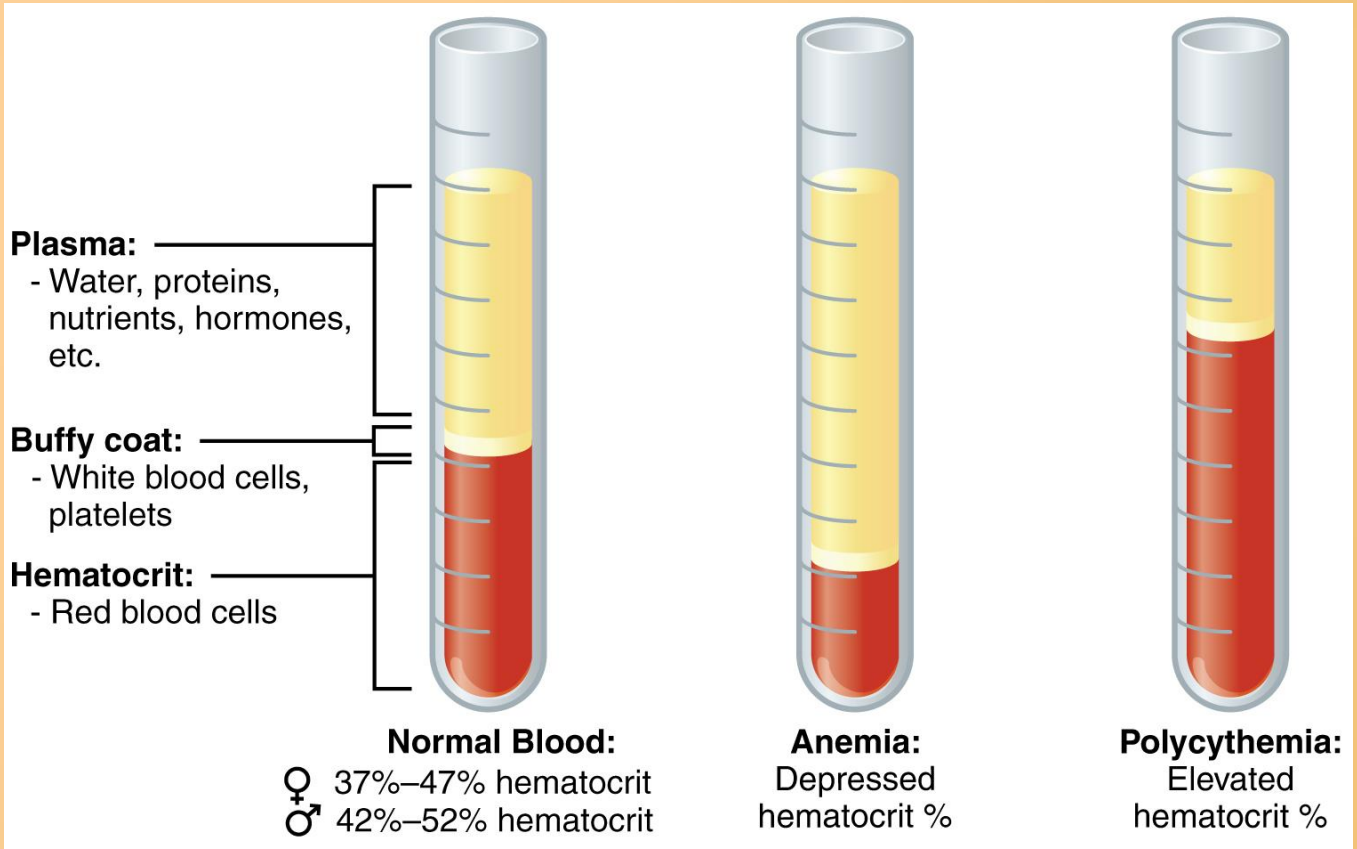
Red blood cell disorders

- Diseases affecting RBCs are among the most common illnesses worldwide.
  - ✓ RBC disorders are the most common human genetic diseases,
  - ✓ Acquired anemias affect up to 25% of the world's population.

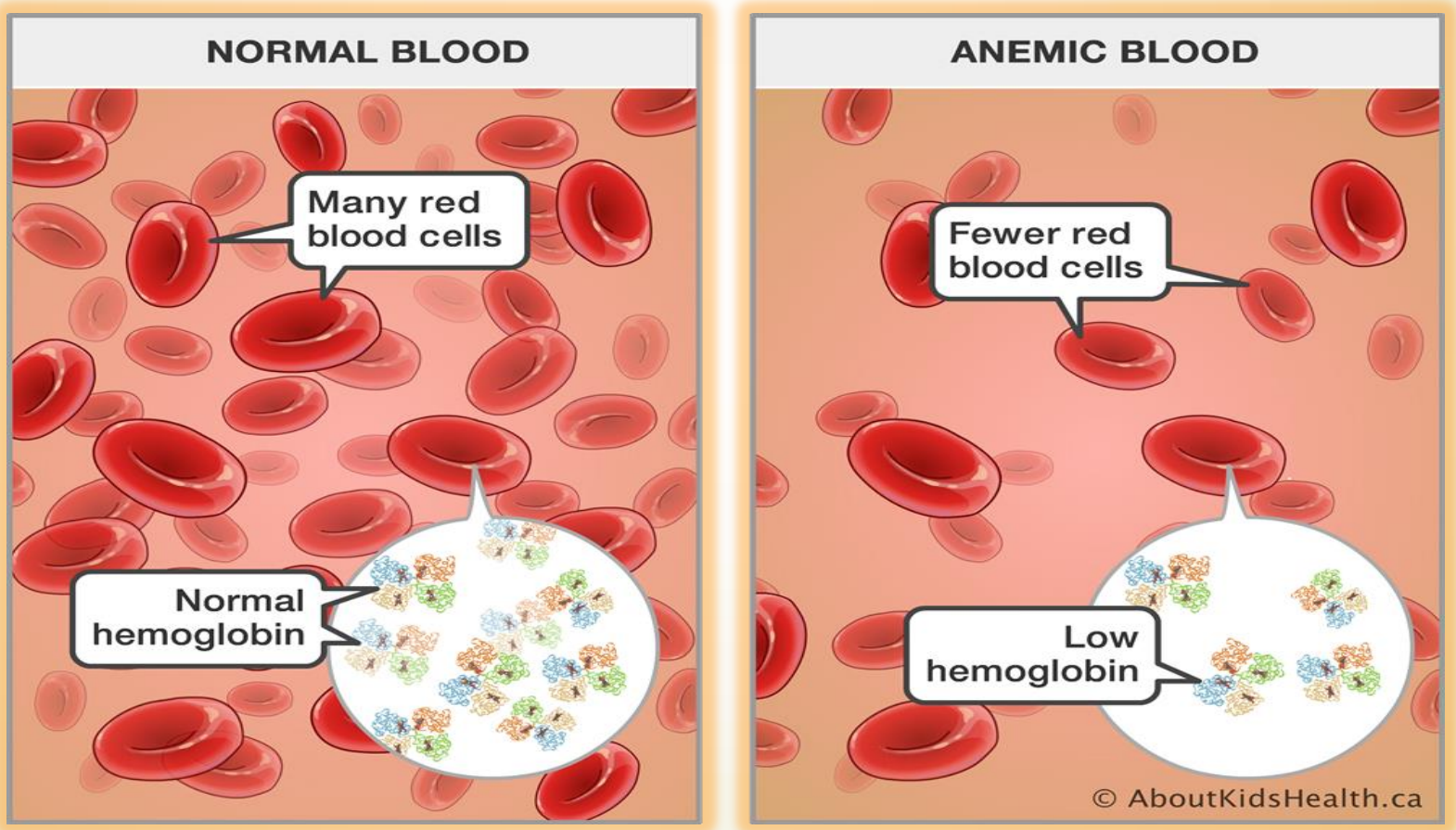


Red blood cell disorders

- Diseases affecting RBCs:
  1. Erythrocytopenia (Anemia)
  2. Erythrocytosis (Polycythemia)



A Practical Approach to Anemias



Anemia

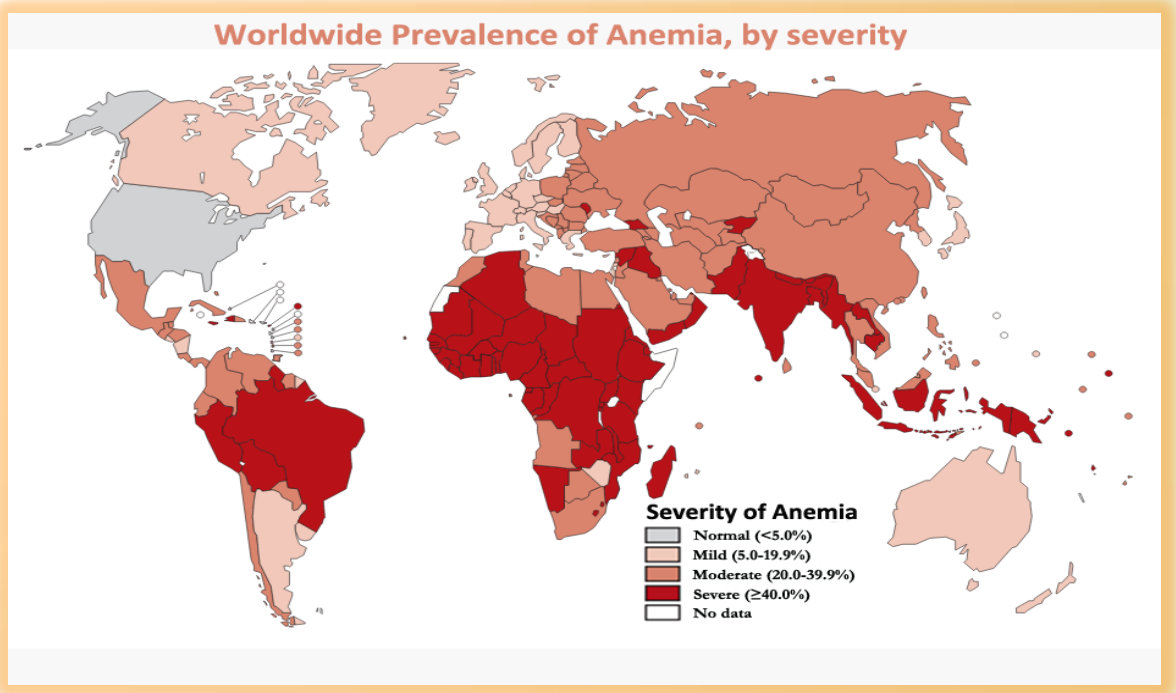
- **Anemia** difinition:
  - functionally ☞ ↓ competence of blood to carry O2
  - in clinical medicine ☞ ↓ Hb concentration < lower limit of 95% reference interval for the individual's age, sex, and geographic location
    - ✓ 2.5% of normal individuals will be classified as anemic and conversely

- **Anemia:**
  - ✓ Hb< 13.5 g/dL in adult males (M), Hb< 11.5 g/dL in adult females (F)
  - ✓ Hb< 11.0 g/dL in 2 years to puberty
  - ✓ Hb< 14.0 g/dL in newborn infants

Anemia

- WHO defines anemia in **adults** as: Hb< 13 g/dL in M or Hb< 12 g/dL in F
  - ✓ On this basis, anemia was estimated ~ 33% of global population (in 2010)

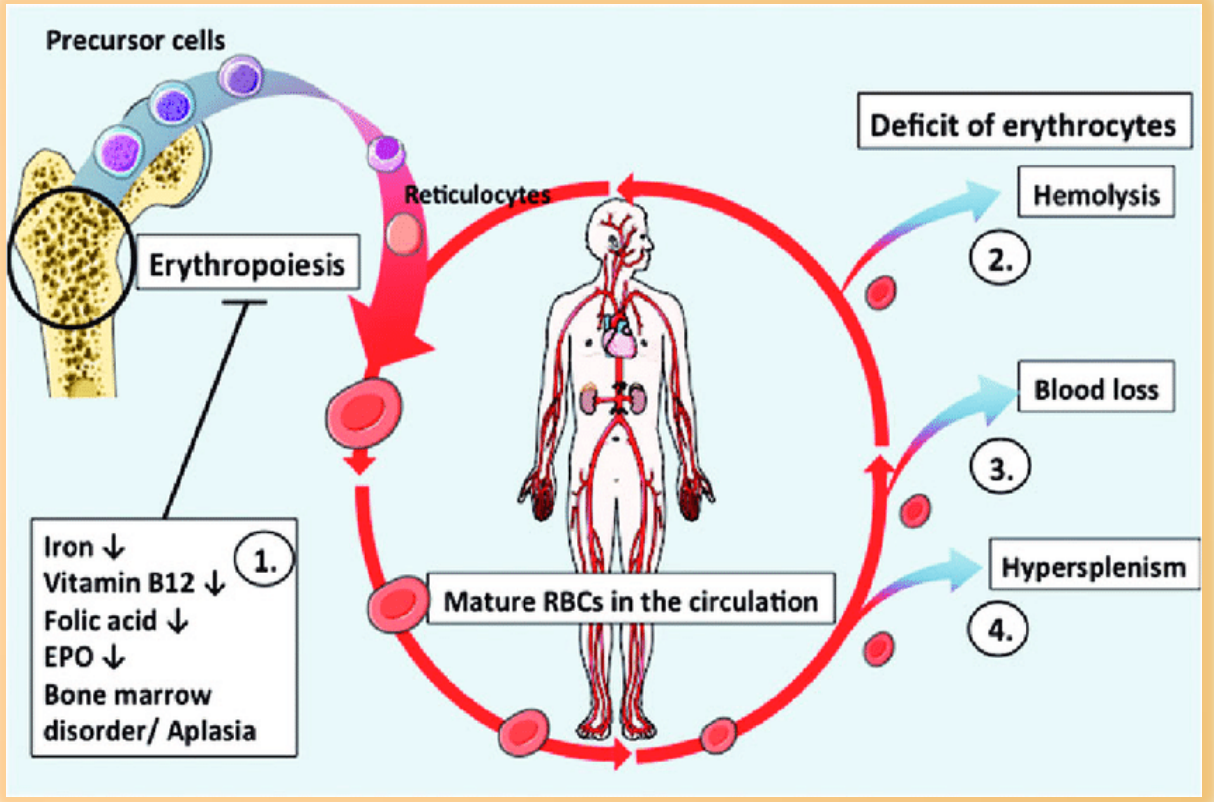
- **The main causes of anemia:**
  - ✓ iron deficiency (hookworm, schistosomiasis)
  - ✓ sickle cell diseases
  - ✓ thalassemia
  - ✓ malaria
  - ✓ anemia of chronic disorders (ACD)



- **Prevalence:**
  - ❖ F > M at all ages
  - ❖ most frequent in children <5 years old
  - ❖ most frequent in South Asia, and Central, West and East of Africa

Anemia

- Anemia can develop if:
  1. BM erythrocyte production is impaired or
  2. RBC loss or destruction exceeds the maximal capacity of BM production



- BM can compensate ↓ RBC survival ☞ with ↑ production to a level 5–8 times normal (maximal functional capacity of BM).
  - ✓ when RBC life span ↓ to ~18 days → BM compensation is inadequate and anemia develops

Screening for anemia

- is usually made from the CBC results ☞ generally relies on Hb/Hct:
  - ✓ In general, Hct / Hb both move ↑ and ↓ together
  - ✓ By contrast, changes in RBC count do not always parallel changes in Hct/Hb
    - ❖ In a patient with Thal trait: ↓ Hct or ↓ Hb + N or ↑ RBC count
  - ○ Sometimes, Hb/Hct can be misleading ☞ as changes in Hct /Hb can due to altered plasma volume also

Interpretation of Hb Concentrations

Hb concentration determined by:

❶ Total circulating **plasma volume**

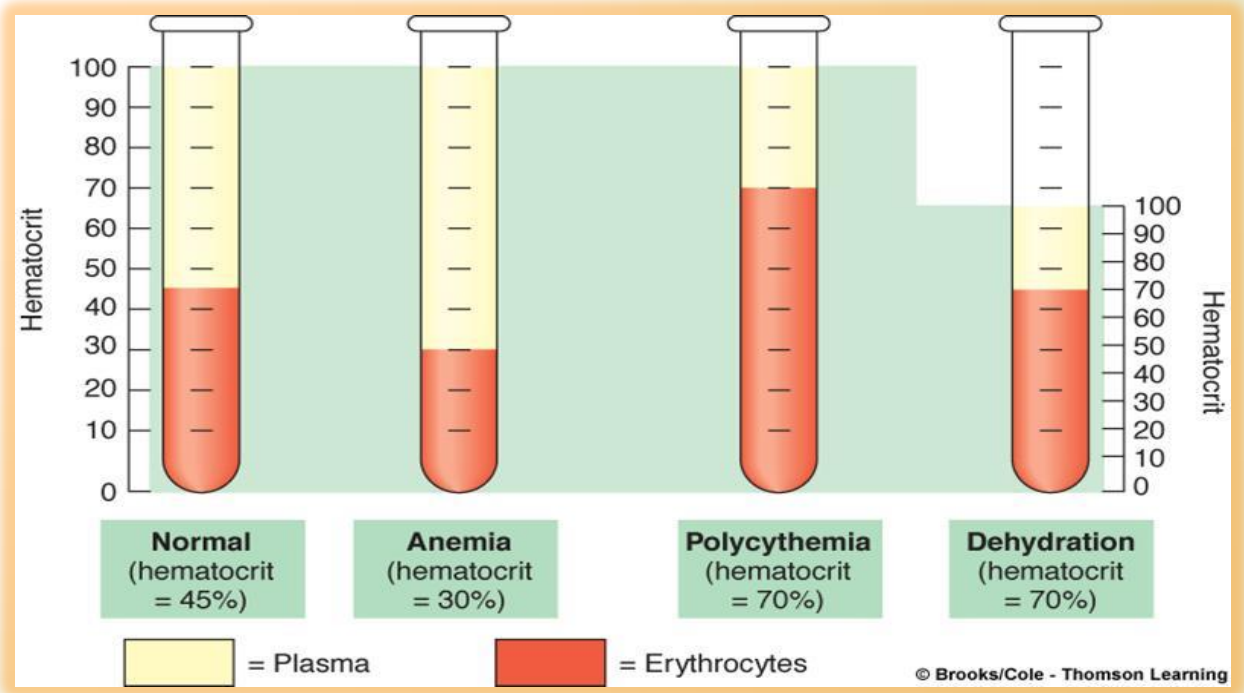
- ↓ **plasma volume** (dehydration) → may mask anemia or even cause polycythemia (apparent, pseudo)
- ↑ **plasma volume** (splenomegaly or pregnancy) → may cause anemia even with normal total circulating RBC mass

❷ Total circulating **RBC (Hb) mass**

① ↓ **Hb**: anemia, ② ↑ **Hb**: polycythemia

Anemia:

1. **Relative** (↑ plasma volume)
   - Pregnancy, macroglobulinemia,
   - in postflight astronauts
2. **Absolute** (↓ RBC mass):
   - ↓ RBC production
   - ↑ RBC destruction (or blood loss)



Diagnosis of Anemia– Lab investigation

III. Laboratory investigation
- A. Erythrocyte count
- B. Hemoglobin
- C. Hematocrit
- D. Erythrocyte indices: MCV, MCH, MCHC
- E. Reticulocyte count, reticulocyte production index (RPI), corrected reticulocyte count, CHr or Ret-He, IRF
- F. Blood smear examination
- G. Leukocyte and platelet quantitative and qualitative examination
- H. Peripheral blood smear evaluation for presence of sphero-cytes, schistocytes and other poikilocytes, and erythrocyte inclusions
- I. Tests to measure erythrocyte destruction depending on other information available: serum bilirubin, haptoglobin, hemopexin, lactate dehydrogenase (LD), methemalbumin, urine hemosiderin, fecal and urine urobilinogen, blood in urine, expired CO
- J. Bone marrow examination (depending upon results of other laboratory tests and patient clinical data)

Diagnosis of Anemia– Lab investigation

- The initial screening test is the CBC
  - Depending on CBC results → additional tests can be suggested:
    - ✓ Retic count, bilirubin, and PBS exam (for abnormal cell morphology)
    - ✓ Urine (UA) and stool (SE) ☞ for the presence of blood

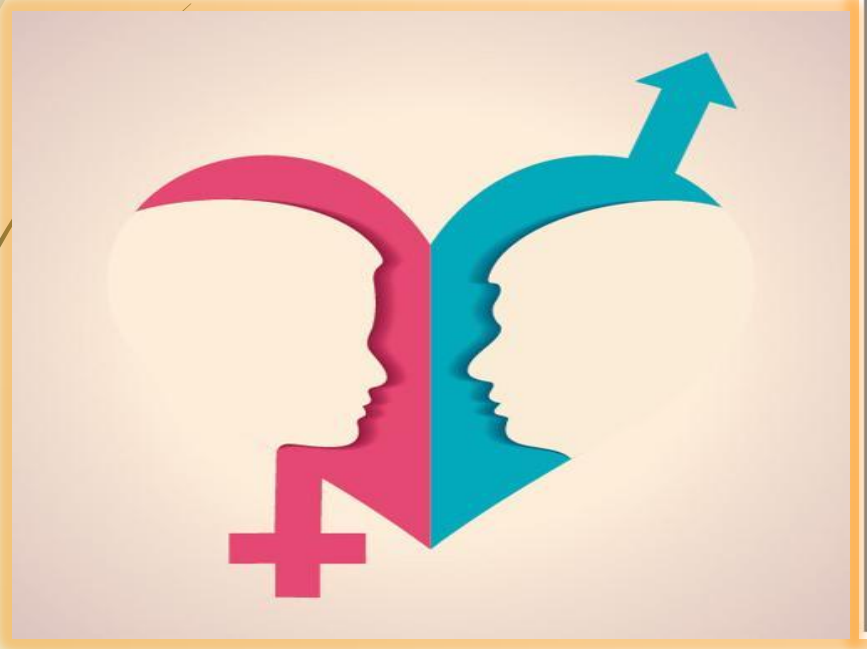
Lab investigation– RBC, Hb, Hct

- RBC, Hb / Hct → to screen for presence of anemia:
  - ✓ ↓ in ≥1 of these parameters → followed by other Lab tests
- The CDC recommended → cutoff values for diagnosis of anemia according to age and sex.

CDC: Centers for Disease Control and Prevention

Lab investigation– RBC, Hb, Hct

- Hb/ Hct Cutoffs for diagnosis of anemia in Children, Males and nonpregnant Females.



Age (yrs) by Sex	Hb (g/dL)	Hct (%)
Both sexes		
1–1.9	11.0	33.0
2–4.9	11.2	34.0
5–7.9	11.4	34.5
8–11.9	11.6	35.0
Female		
12–14.9	11.8	35.5
15–17.9	12.0	36.0
≥18	12.0	36.0
Male		
12–14.9	12.3	37.0
15–17.9	12.6	38.0
≥18	13.6	41.0

Based on fifth percentile values from the Second National Health and Nutrition Examination survey conducted after excluding persons with a higher likelihood of iron deficiency.

Centers for Disease Control (CDC). CDC criteria for anemia in children and childbearing-aged women. *MMWR Morb Mortal Wkly Rep*. 1989;38(22):400–4.

Lab investigation– RBC, Hb, Hct

- Upward adjustments for Hb/Hct cutoff values should be utilized for individuals living at high **altitudes**.

Altitude (ft)	Hb (g/dL)	Hct (%)
<3000	—	—
3000–3999	+0.2	+0.5
4000–4999	+0.3	+1.0
5000–5999	+0.5	+1.5
6000–6999	+0.7	+2.0
7000–7999	+1.0	+3.0
8000–8999	+1.3	+4.0
9000–9999	+1.6	+5.0
>10,000	+2.0	+6.0

Centers for Disease Control (CDC). CDC criteria for anemia in children and childbearing-aged women. *MMWR Morb Mortal Wkly Rep*. 1989;38(22):400–4.

Lab investigation– RBC, Hb, Hct

- There is a direct dose–response relationship between the amount **smoking** and Hb level.

Characteristic	Hb (g/dL)	Hct (%)
Nonsmoker	—	—
Smoker (all)	+0.3	+1.0
½–1 pack/day	+0.3	+1.0
1–2 packs/day	+0.5	+1.5
>2 packs/day	+0.7	+2.0

Centers for Disease Control (CDC). CDC criteria for anemia in children and childbearing-aged women. *MMWR Morb Mortal Wkly Rep*. 1989;38(22):400–4.

Lab investigation– RBC, Hb, Hct

- Hb/Hct values also vary in **pregnancy** ☞ a gradual ↓ in the first 2 trimesters and a ↑ during the third trimester.

	Gestation (wks)/Trimester							
	12/1†	16/2	20/2†	24/2	28/3	32/3†	36/3	40/Term
Mean Hb (g/dL)	12.2	11.8	11.6	11.6	11.8	12.1	12.5	12.9
5th percentile Hb values (g/dL)	11.0	10.6	10.5	10.5	10.7	11.0	11.4	11.9
Equivalent 5th percentile Hct values (%)†	33.0	32.0	32.0	32.0	32.0	33.0	34.0	36.0

[a] Based on pooled data from four European surveys of healthy women taking iron supplements. Hb values adapted for the trimester-specific cutoffs
†Hematocrit
From Centers for Disease Control (CDC). CDC criteria for anemia in children and childbearing-aged women. *MMWR Morb Mortal Wkly Rep.* 1989;38(22):400–4.

Lab investigation– RBC, Hb, Hct

- Anemia is prevalent in **elderly** persons ☞ but it not a normal part of aging.
  - ✓ After age 65 → ↑ prevalence of anemia (11% in M; 10.2% in F)
    - ☞ prevalence for those in nursing homes is higher.
  - ✓ The highest prevalence ☞ in ages > 85 years (26% of M and 20% of F). In this group:
    1. 1/3 was due to blood loss or nutritional deficiency,
    2. 1/3 was due to ACD, inflammation, or chronic renal failure,
    3. 1/3 was unexplained ☞ can be due to multiple causes.

ACD: anemia of chronic disease

Lab investigation- RBC, Hb, Hct

- Variations in Hb due to **blood-drawing** techniques.
  - ✓ in upright position compared with supine ☞ Hb values are ~0.7 g/dL higher

- Prolonged vasoconstriction by **tourniquet** → cause hemoconcentration of sample and elevate Hb value.

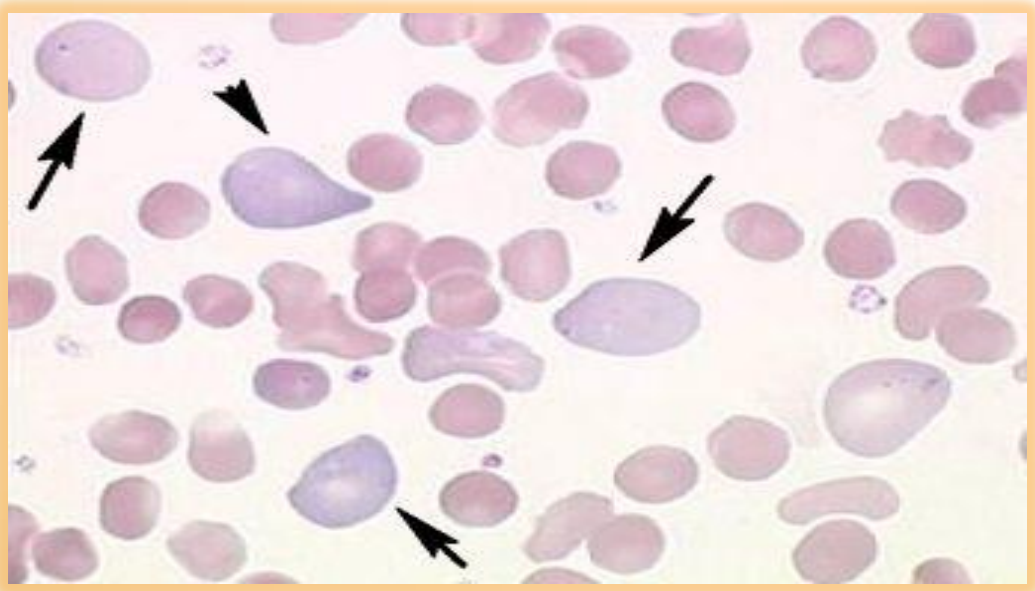
Lab investigation- RBC Indices

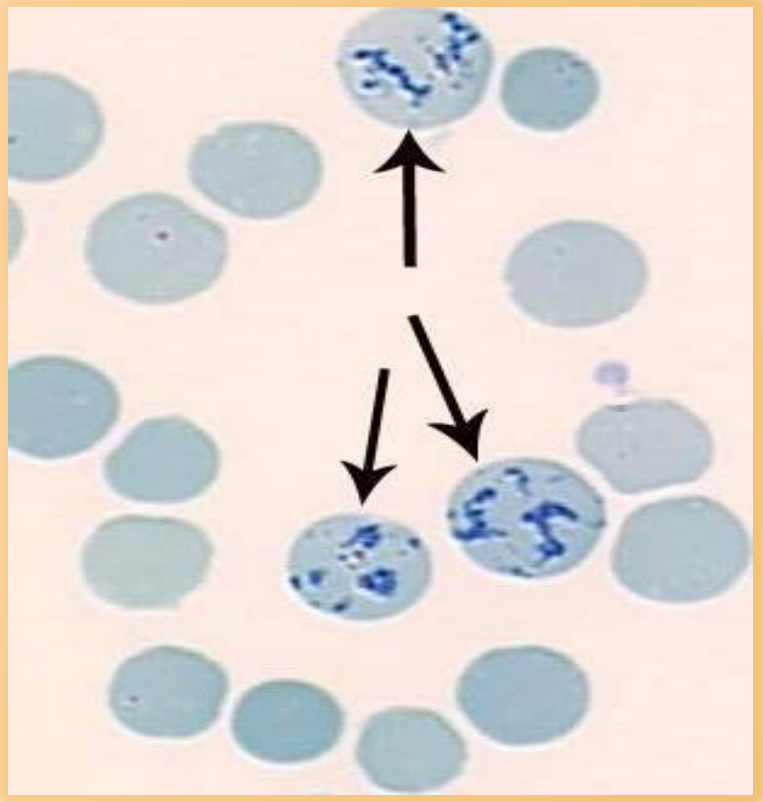
- **RBC indices** (MCV, MCH, MCHC, RDW) → give important clues to the pathophysiology of anemia
  ☞ help to direct reflex testing
  - ✓ Microcytic hypochromic cells → highly suggestive of IDA
  - ✓ Macrocytic normochromic cells → associated with B12 or folate deficiency

IDA: iron-deficiency anemia

Lab investigation– Reticulocyte Count

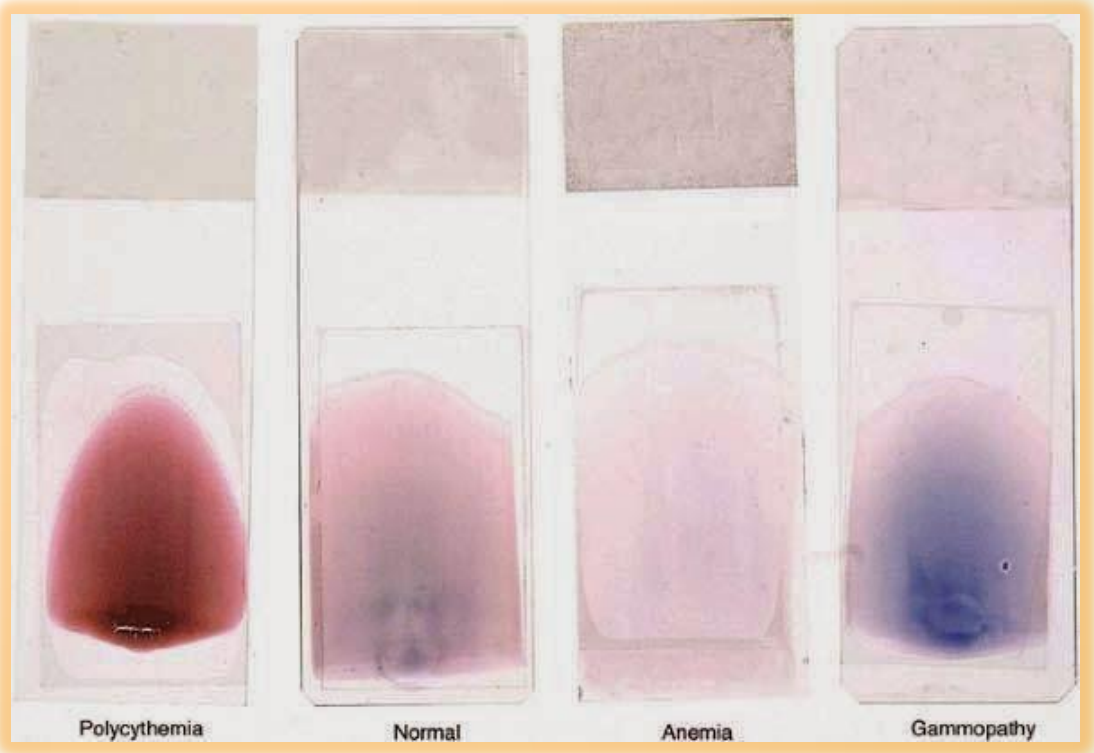
- **Retic** count → indicates the degree of effective BM erythropoietic activity
  - ✓ is helpful in directing investigation of anemia (assists in classification of anemia)
  - ✓ is useful in monitoring anemia and response to therapy





Lab investigation– Blood Smear Examination

- Various pathological conditions (intrinsic or extrinsic) can alter RBC's morphology
  - ✓ careful examination of **PBS** assists in diagnosing the type of anemia in ~25% of cases.



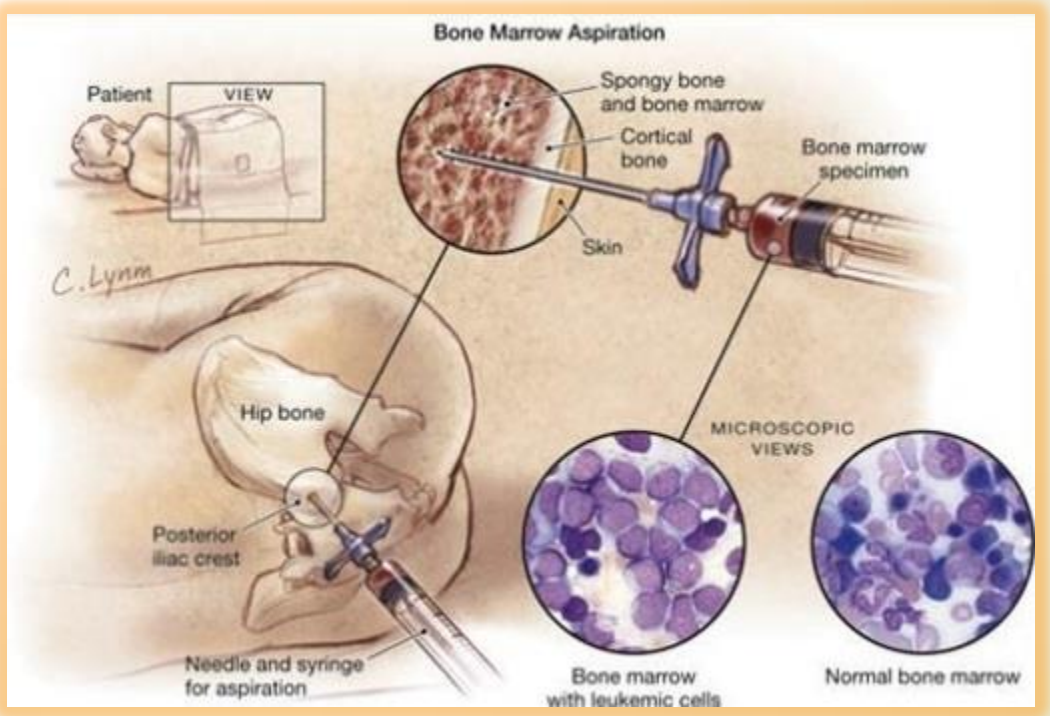
PBS: peripheral blood smear

Lab investigation– WBC and PLT Abnormalities

- **WBC & PLT counts**
  - ✓ helps to distinguish 'pure' anemia from 'pancytopenia'
- Pancytopenia suggests:
  - ✓ a general BM defect (e.g. Hypoplasia, Infiltration)
  - ✓ a general destruction of cells (e.g. hypersplenism)
- in anemias caused by hemolysis or hemorrhage→ ↑ Neut & PLT counts
- in Infections and Leukemia → ↑ leucocyte count + abnormal leucocytes precursors

Lab investigation- BM examination

- **BM examination** usually is not necessary to determine the cause of an anemia.
  - it can provide supplemental diagnostic information, when other Lab tests are not conclusive.
    - ✓ BM evaluation in hypoproliferative anemias → can reveal myelodysplasia or infiltration with malignant cells or granulomas.
    - ✓ Erythroid hyperplasia (with ↓ fat & consequently ↓ M:E) → is more pronounced in Hemolytic anemia than in non-hemolytic anemias



Classification of Anemias

- Purpose:
  - ✓ to assist physician in identifying the cause by using Lab results in addition to other clinical data
  - ✓ also is useful to Lab professionals when they correlate various test results for accuracy and make suggestions for additional reflex testing

- Anemias can be classified by:
  1. Morphology
  2. Pathophysiology

Anemia Classification

Morphologic & Pathophysiologic classifications of Anemias

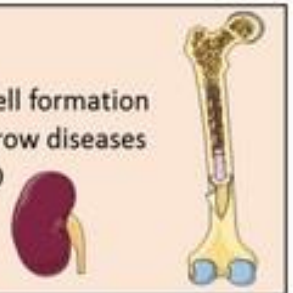
A. Morphology → MCV
B. Hb concentration → MCH
C. Etiology

Hypochromic, Microcytic
MCV ↓, MCH ↓

Macrocytic
MCV ↑

Normochromic, Normocytic
MCV =, MCH =

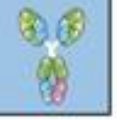
1. Impaired erythropoiesis
- Disorder of cell proliferation → Lack of vitamin B12 and folic acid
- Disorder of cell maturation →Lack of/ disturbed adsorption of iron
- Disorder of cell formation → Bone marrow diseases → lack of EPO

2. RBC depletion/ hemolysis

Intraerythrocytic	Extraerythrocytic
Hemoglobinopathy	Genetic disease/ Chronic disease
Cytoskeleton disorder	Toxic (Drugs)
Defect of metabolic enzymes	Autoimmune/ Infectious
Disorder of redox regulation	Autoimmun/ Antibody-related



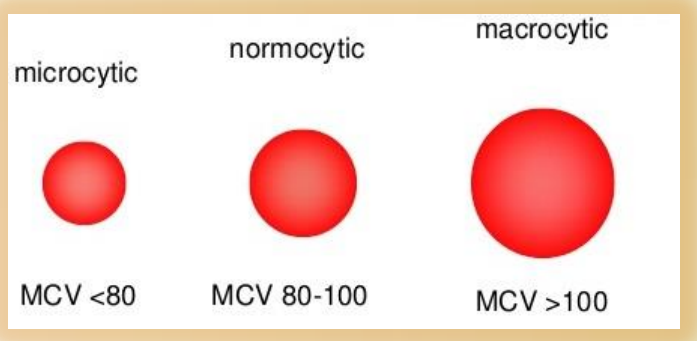
3. Loss of RBCs


Acute blood loss — Chronic blood loss

4. Impaired RBC distribution
Hypersplenism

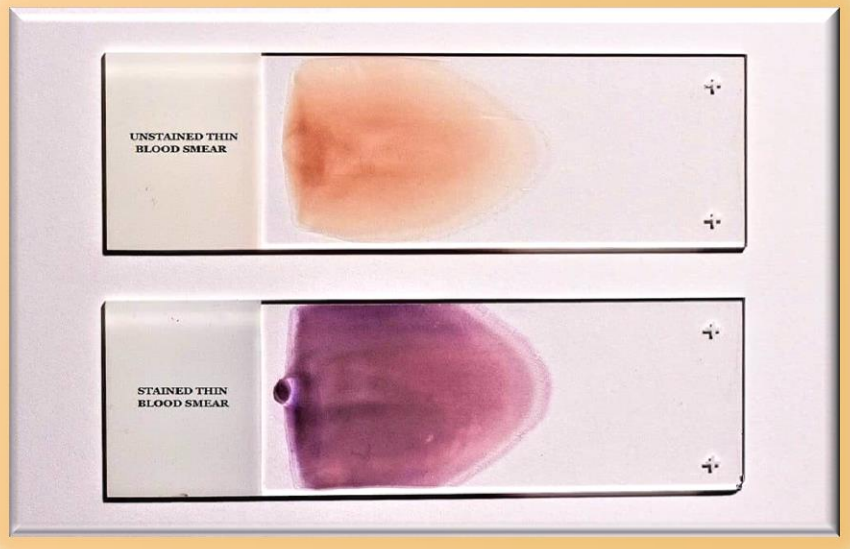
Anemia- Morphologic Classification

- The first step in approaching anemia is to classify based on RBC volume (MCV):
  1. Microcytic (MCV, <80 fL),
  2. Normocytic (MCV, 80-100 fL),
  3. Macrocytic (MCV, >100 fL)



✓ This exercise markedly narrows the differential diagnosis that needs to be considered in each patient.

- It strongly recommend obtaining a PBS during the initial evaluation of anemia (regardless of subtype)



Approach to Microcytic Anemia

- The most common anemias in clinical practice are the microcytic anemias.
- a simple acronym summarizes the causes of microcytic anemia: TAILS:
  1. T (thalassemia and the thalassemic hemoglobinopathies)
  2. A (anemia of chronic disease; ACD)
  3. I (iron deficiency; IDA)
  4. L (lead poisoning)
  5. S (congenital sideroblastic anemia; SA)

- Expressed in order of frequency:

  ① IDA: the most common microcytic anemia,

  ②③ (depending on one's patient population) ACD or thalassemia,

  ④ Lead poisoning (a normocytic anemia) → classically found in association with IDA ⇒ usually listed with the microcytic anemias

  ⑤ Congenital sideroblastic anemia.

Microcytic anemia

- The 3 major diagnostic possibilities for microcytic anemia are:
  1. Iron deficiency anemia (IDA)
  2. Thalassemia
  3. Anemia of chronic disease (ACD)

☑ Lead poisoning and SA ☞ are not prevalent enough for routine consideration

Category of anemia	Differential diagnosis	CBC clues	PBS clues
Microcytic	Iron deficiency anemia	Increased RDW Thrombocytosis	Anisocytosis Poikilocytosis Elliptocytosis
	Thalassemia	Normal or elevated RBC count Normal or elevated RDW	Polychromasia Target cells Basophilic stippling
	Anemia of chronic disease	Normal RDW	Unremarkable (typically) Rouleaux formation (CD) Myelophthisis (MMM)†

Microcytic anemia

Step 1. Rule Out Iron Deficiency Anemia

- Since the most common of the microcytic anemias is IDA ☞ it recommend determination of serum ferritin level as initial step for all patients with microcytic anemia:

① **Low ferritin** level → is diagnostic of IDA

- ✓ contrary to current dogma regarding acute phase reaction ☞ a diagnosis of IDA is unlikely in the presence of a persistently N or ↑ serum ferritin level.
- ✓ in general, it **not recommend** either other serum iron studies (serum iron, TIBC, transferrin saturation) or BM biopsy for evaluation of IDA.
  - Instead, a limited treatment trial with iron supplementation is both a cost-effective & definitive way of addressing the issue in equivocal cases.

IDA: Iron deficiency anemia / TIBC: total iron-binding capacity

Microcytic anemia

- **Important notes:**

☑ microcytic anemia associated with ↑ RDW → favors a diagnosis of IDA over that of ACD

☑ microcytic anemia associated with ↑ RBC count → is characteristic of thalassemia trait

☑ Microcytosis without anemia → could occur in ① thalassemia trait ② in polycythemia associated with iron deficiency.

☑ PBS in IDA usually shows anisocytosis and poikilocytosis → in severe cases, cigarshaped RBCs and elliptocytes are characteristically present.

☑ Polychromasia, basophilic stippling, and target cells → are characteristic features in thalassemia.

☑ IDA → may be associated with reactive thrombocytosis.

Microcytic anemia

Step 2. Evaluation of Microcytic Anemia with Normal Serum Ferritin

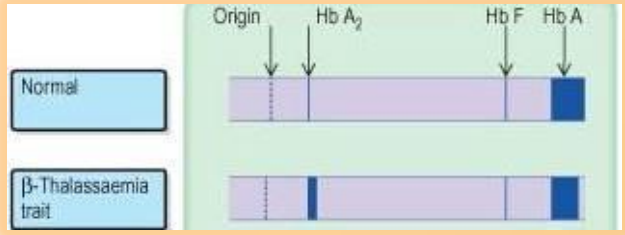
② **Normal ferritin** level → the next step is to determine whether the microcytosis is new or previously recognized?

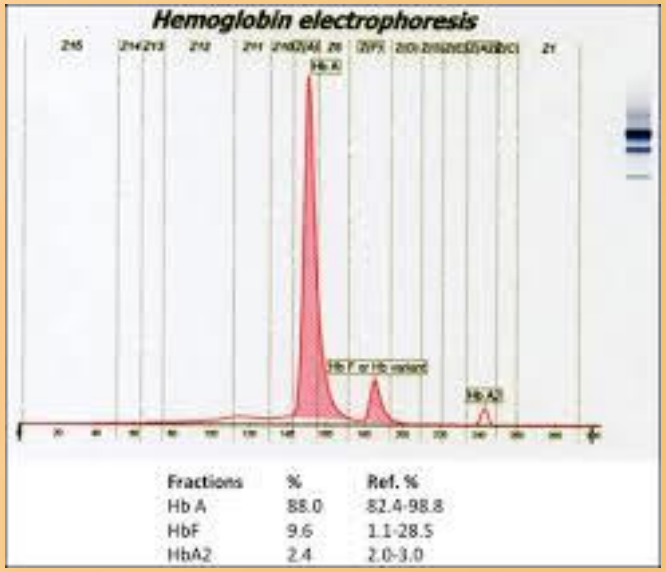
- ✓ in patients with **chronic microcytosis** ☞ a diagnosis of thalassemia should be considered → Hb electrophoresis should be ordered as the initial test.
- ✓ If the microcytosis is **new** ☞ a nonthalassemic condition associated with acquired microcytosis is a possibility.

Microcytic anemia

- **Hb electrophoresis** → the initial test of choice for investigation of thalassemia (α-, β-Thal, and structurally abnormal globin chain Thal).
  - ☑ Hb electrophoresis does not always detect presence of thalassemia ⇒ utility of genetic testing
    - ✓ a hematology consultation may be necessary for accurate interpretation of results

	Hb A	Hb F	Hb A_2
Structure	$\alpha_2\beta_2$	$\alpha_2\gamma_2$	$\alpha_2\delta_2$
Normal (%)	96–98	0.5–0.8	1.5–3.2





- Hb electrophoresis results:
  1. Normal → in α-thal trait
  2. Abnormal → in β-thal trait & other thal syndromes (↑ Hb A2 to 3-6%)
     - ✓ if IDA coexists (β-thal trait) ☞ expected ↑ Hb A2 may not occur ⇒ a normal Hb A2 level may not exclude the possibility of β-thal trait → unless a simultaneously measured normal serum ferritin level is documented.

Microcytic anemia

- **α-Thal** ☞ Genetic testing (PCR–based DNA tests and Southern blot analysis) can reveal the molecular defect.

  ☑ However, a genetic counseling can be initiated on the basis of family history and ethnic origin and without resorting to DNA testing.

- **β-Thal** ☞ a slight or moderate ↑ in Hb F may also be seen in β-thal trait

  ☑ in general, Hb electrophoresis is often adequate for evaluating β-thal, and genetic testing may be unnecessary.

- **Structurally Abnormal Globin Chain Thalassemia.**

  - Some structural Hb-pathies can produce a thalassemic (microcytic) phenotype as a result of ↓ globin synthesis (Hb E, Hb Lepore, Hb CS)

    ✓ These thalassemic syndromes → usually are identified by routine Hb electrophoresis ⇒ genetic testing may not be required.

Microcytic anemia

Nonthalassemic (Acquried), non-IDA microcytic anemia

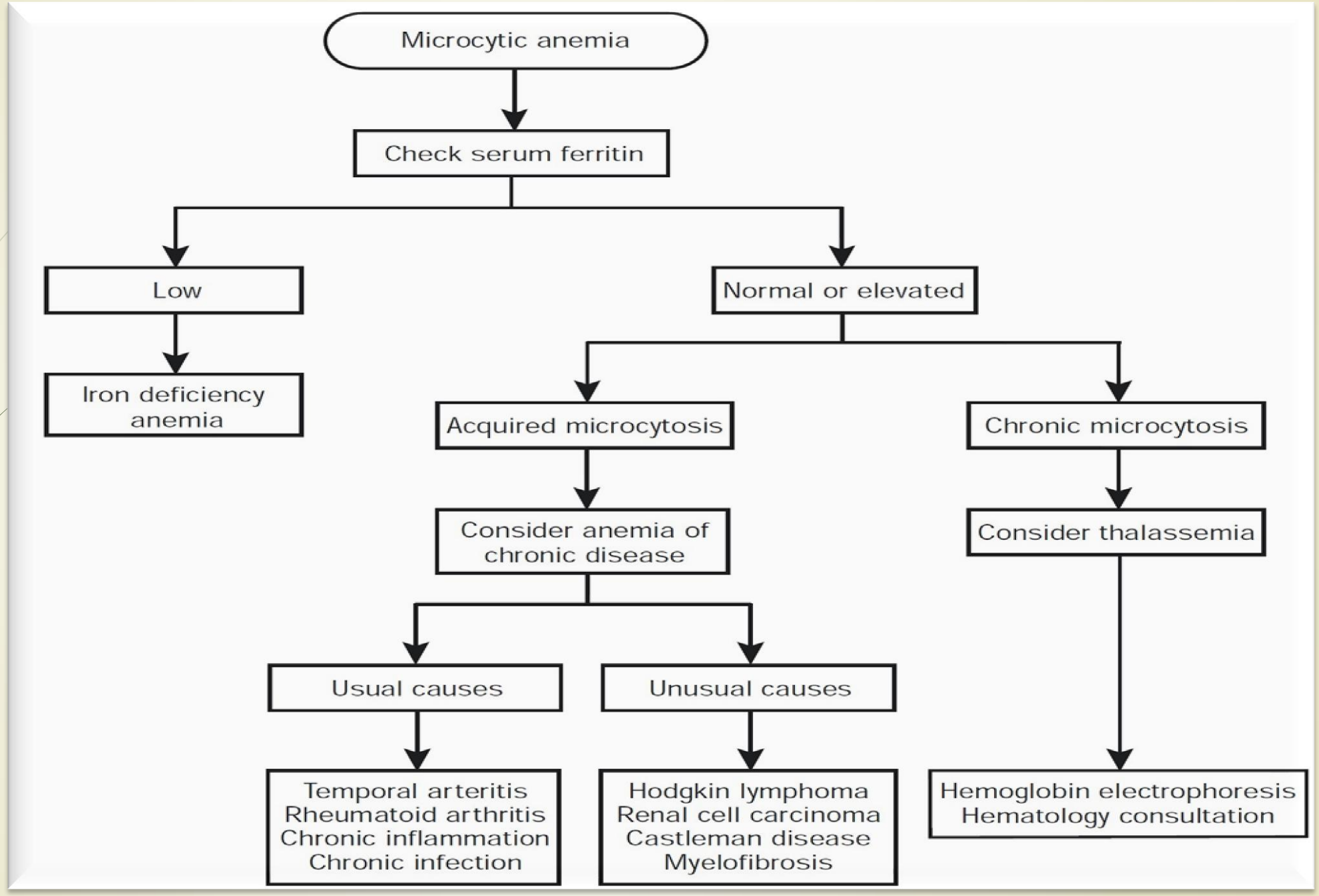
- The differential diagnosis includes ACD and Sideroblastic anemia (SA).
  - ✓ SA: a rare disorder ☞ characterized by ↑ RDW, dimorphic RBCs, and BM ring sideroblasts.

☑ Acquired, non-IDA microcytic anemia → is labeled as microcytic ACD ☞ is indicative of an underlying systemic disease (usual & unusual)

- ✓ Anemia in ACD is usually normocytic ☞ but in some systemic diseases can be microcytic anemia.

- Further clinical and Lab investigation in this instance is dictated by:
  1. patient history
  2. findings from physical examination
  3. examination of PBS

ACD: Anemia of chronic disease


Microcytic anemia
Check serum ferritin
Low
Iron deficiency anemia
Normal or elevated
Acquired microcytosis
Consider anemia of chronic disease
Usual causes
Temporal arteritis
Rheumatoid arthritis
Chronic inflammation
Chronic infection
Unusual causes
Hodgkin lymphoma
Renal cell carcinoma
Castleman disease
Myelofibrosis
Chronic microcytosis
Consider thalassemia
Hemoglobin electrophoresis
Hematology consultation

Normocytic anemia

Category of anemia	Differential diagnosis	CBC clues	PBS clues
Normocytic	Bleeding	Usually unremarkable	Polychromasia
	Nutritional anemia	Increased RDW	Anisocytosis
			Dimorphic RBCs
	Anemia of renal insufficiency	Normal RDW	Usually unremarkable
	Hemolysis	Normal or elevated RDW	Polychromasia
		Thrombocytosis	Spherocytes
			Schistocytes
			Bite cells
	Anemia of chronic disease	Normal RDW	Unremarkable
	A primary bone marrow disorder	Increased RDW	Dimorphic RBCs (MDS)
		Other cytopenias	Pseudo Pelger-Huët anomaly (MDS)
		Monocytosis	Oval macrocytes (MDS)
		Leukocytosis	Myelophthisis (MMM)†
		Thrombocytosis	Rouleaux (myeloma)
		Abnormal differential	Blasts (acute leukemia)
			Presence of abnormal cells

Normocytic anemia

Step 1. Rule Out Readily Treatable Causes

- The first step in approaching normocytic anemia → to exclude potentially treatable causes from others ☞ including:
  1. Anemia due to bleeding,
  2. Nutritional anemia,
  3. Anemia of renal insufficiency,
  4. Hemolytic anemia

- Patient history → is key in implicating **bleeding** as a cause of anemia
  - if indicated ☞ fecal occult blood (OB) test can be ordered

Normocytic anemia

- **Nutritional anemia**
  - both iron and B12/folate deficiencies are possible causes of "normocytic" anemia (despite their usual association with micro- & macrocytic anemia, respectively)
    - Therefore, the initial investigation of normocytic anemia should include determination of both serum ferritin and serum B12/ folate levels

- **Anemia of renal insufficiency**
  - is addressed easily by checking serum creatinine level.
  - Anemia is associated with: an unremarkable PBS and an inappropriately normal serum EPO level.
    - ✓ in advanced kidney disease (serum creatinine, >3 mg/dL) ☞ anemia is severe and symptomatic

- If initial tests are unrevealing → the possibility of hemolyytic anemia (HA) should be considered.

Normocytic anemia

- **Hemolytic anemia** (HA):
  - is usually normocytic ☞ but can be macrocytic (due to marked reticulocytosis)
    - Initial Lab tests that should be ordered when hemolysis is suspected include:
      - serum levels of Haptoglobin
      - serum levels of LDH
      - indirect Bilirubin
      - Retic count
      - PBS examination

- ✓ None of these tests are able to distinguish among the various causes of HA.

- In general, if: ↓ haptoglobin + ↑ LDH, indirect Bil, Retic count ☞ an **active hemolysis** is suspected

Normocytic anemia

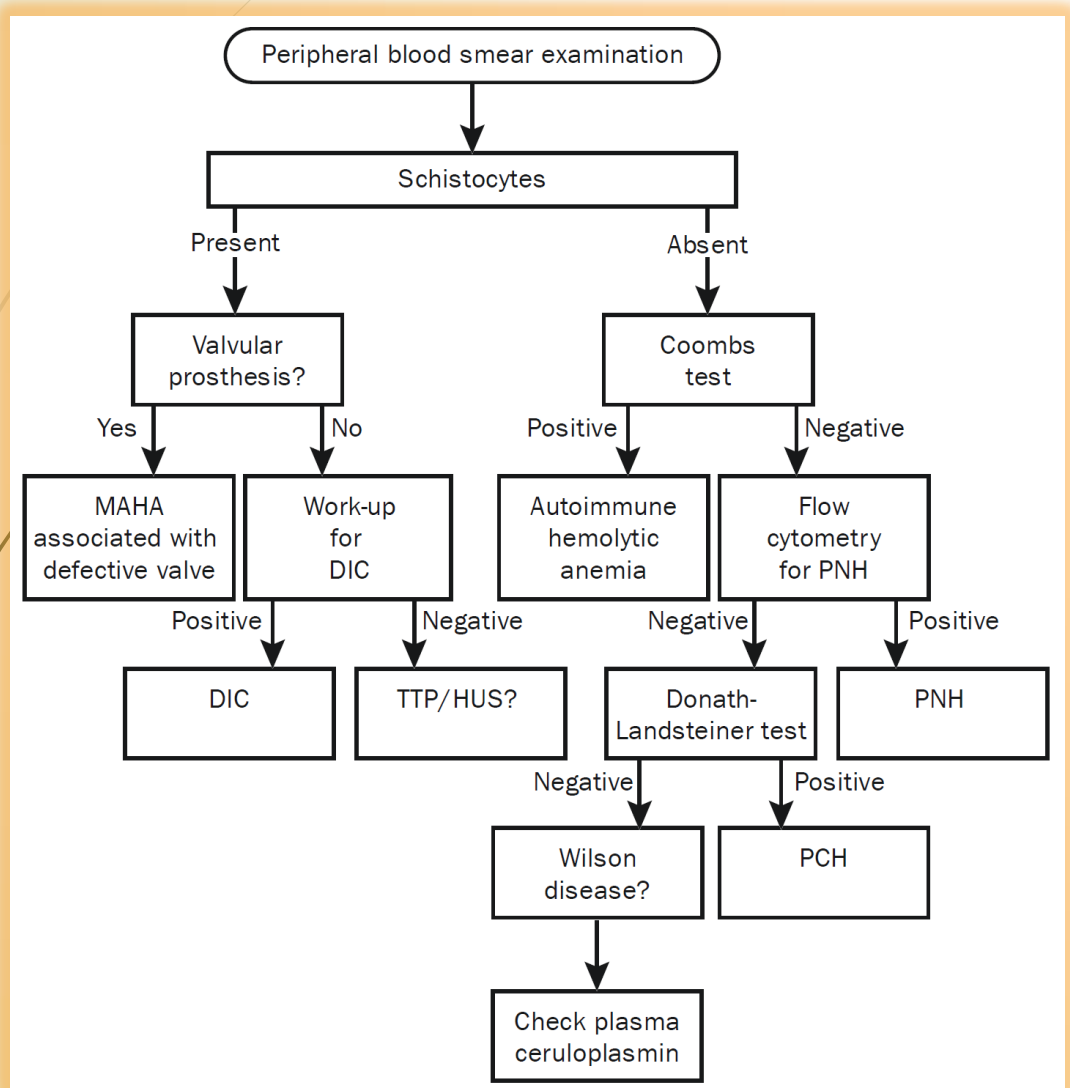
- **Hemolytic anemia** (HA) can be classified in many ways:
  1. One classification ☞ separates causes: that are intrinsic or extrinsic to RBC.
  2. in clinical practice → it may be preferable to first distinguish EV-HA from IV-HA ☞ using urinary hemosiderin test

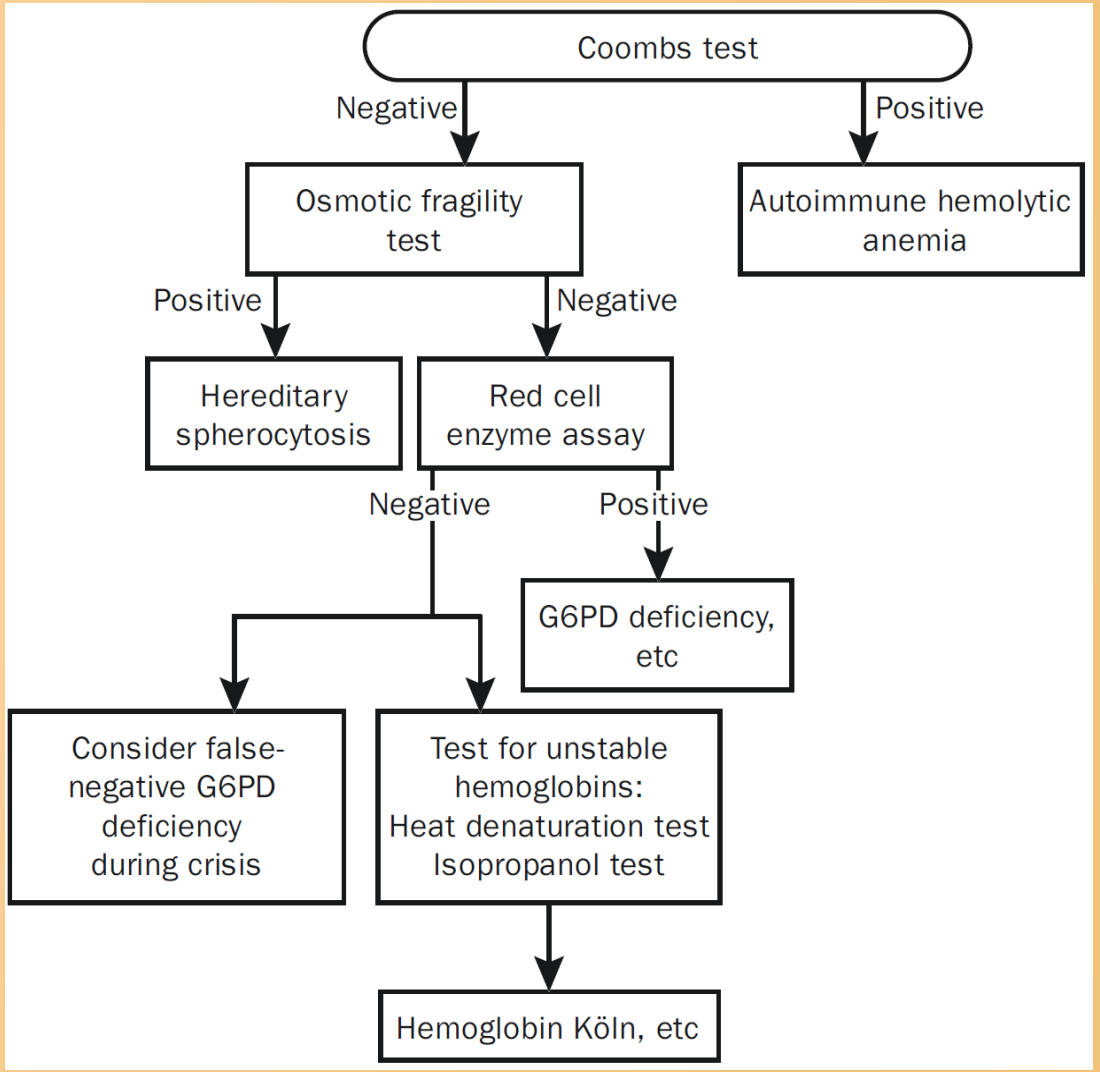
Test	Hemolytic anemias	
	IV-HA	EV-HA
Retic count	↑	↑
LDH	↑	↑
Indirect Bilirubin	↑	↑ or N
Haptoglobin	↓	↓
Urinary Hemosiderin	+	-

- In general:
  - RBC–intrinsic and immune-mediated HA → are extravascular
  - MAHA, infection-associated, and chemical-induced HAs → are intravascular
    - ☑ a drug-induced mechanism always should be considered in any hemolytic process.

IV-HA: Intravascular hemolytic anemia / EV-HA: Extravascular hemolytic anemia / MAHA: microangiopathic HA

Normocytic anemia





Normocytic anemia

Step 2. Normocytic Anemia **Not** Associated With Bleeding, Nutritional Deficiency, Renal Insufficiency, or Hemolysis

- The primary consideration is:
  1. a normocytic ACD
  2. a primary BM disorder
     - ✓ Differentiating between the two is not always easy ☞ Patient history and PBS results provide helpful informations

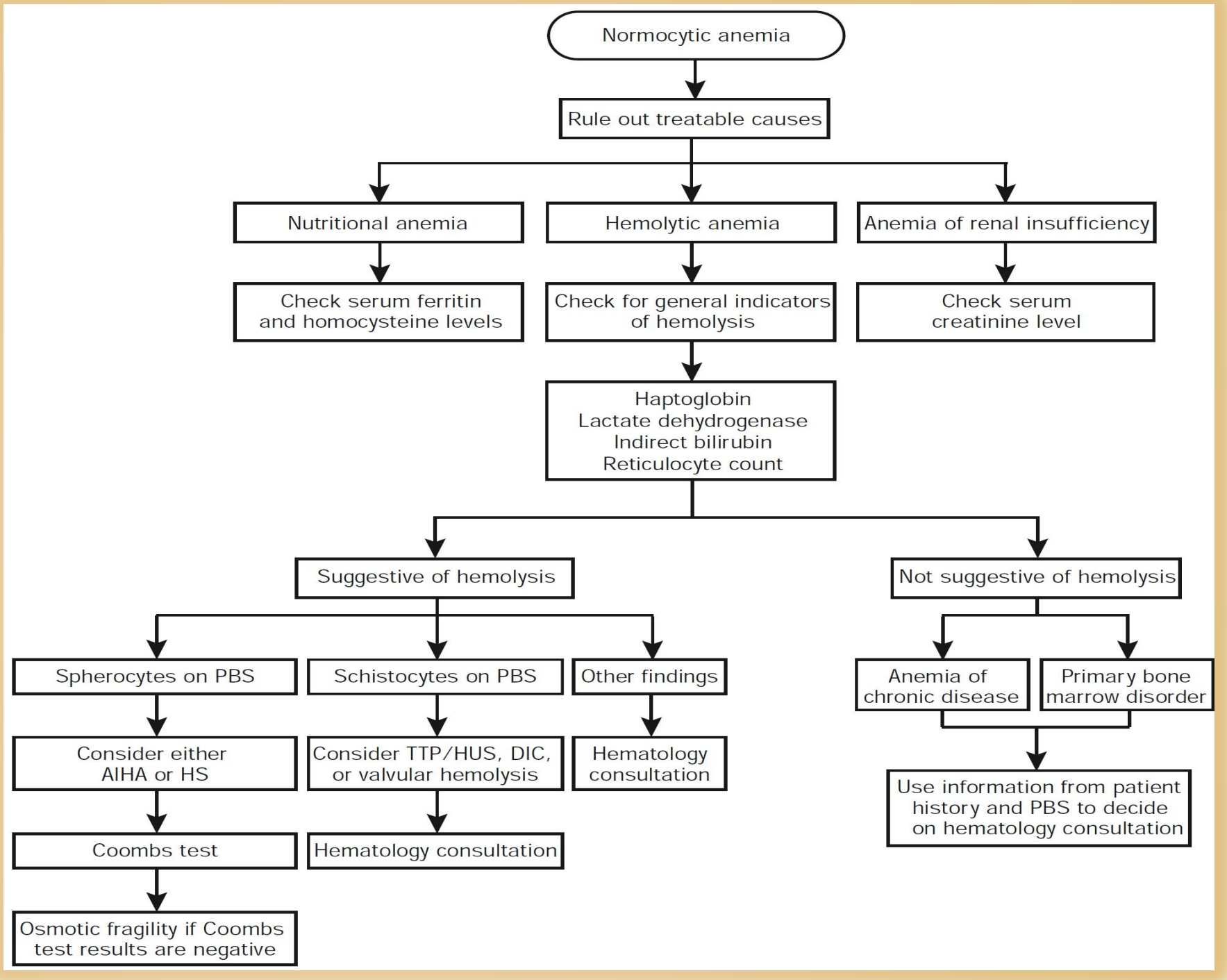
Normocytic anemia

Anemia Due to Primary BM Disorder

- PBS is most helpful in providing clues for a primary BM disease:
  - ✓ In MDS → RDW often is ↑, PBS may show: oval macrocytes, Pseudo-Pelger- Huët anomaly, or monocytosis.
  - ✓ In BM infiltration (PMF, metastatic cancer) → NRBCs and IG are noted.
  - ✓ In MM → RBC rouleaux formation may be seen.
  - ✓ Severe anemia + exremely ↓ Retic count → suggests PRCA or AA.
  - ✓ primary BM disease → often is associated with disorders of WBCs & PLTs.

- ☑ deciding to obtain a BM biopsy or no ☞ depend on: ① likelihood of discovering a primary BM disease ② therapeutic & prognostic value of the derived information. For example:
  - ✓ BM biopsy in an elderly patient with mild anemia is unnecessary ☞ even if PBS suggests a primary hematologic disease (because the results may not affect overall management decisions).
  - ✓ In contrast, a younger patient with a history of chemotherapy or abnormal PBS ☞ should undergo BM biopsy

PRCA: pure red cell aplasia / **AA:** aplastic anemia / **MM:** multiple myeloma


Normocytic anemia
Rule out treatable causes
Nutritional anemia
Hemolytic anemia
Anemia of renal insufficiency
Check serum ferritin and homocysteine levels
Check for general indicators of hemolysis
Check serum creatinine level
Haptoglobin
Lactate dehydrogenase
Indirect bilirubin
Reticulocyte count
Suggestive of hemolysis
Not suggestive of hemolysis
Spherocytes on PBS
Schistocytes on PBS
Other findings
Anemia of chronic disease
Primary bone marrow disorder
Consider either AIHA or HS
Consider TTP/HUS, DIC, or valvular hemolysis
Hematology consultation
Use information from patient history and PBS to decide on hematology consultation
Coombs test
Hematology consultation
Osmotic fragility if Coombs test results are negative

Macrocytic anemia

Category of anemia	Differential diagnosis	CBC clues	PBS clues
Macrocytic	Drug-induced	Increased RDW Marked or mild macrocytosis	Oval macrocytes
	Nutritional	Increased RDW Marked or mild macrocytosis	Oval macrocytes Hypersegmented neutrophils
	MDS or other bone marrow disorder	Increased RDW	Dimorphic RBCs Pseudo Pelger-Huët anomaly cells Oval macrocytes
	Liver disease, alcohol use	Normal RDW Thrombocytopenia	Round macrocytes Target cells
	Hypothyroidism	Normal RDW	Round macrocytes
	Hemolysis	Normal or elevated RDW	Polychromasia

Macrocytic anemia

Step 1. Rule out the Presence of Drugs that Cause Macrocytosis

- The first considerations during evaluation of macrocytic anemia:
  - to exclude certain drugs (eg, hydroxyurea, Methotrexate, Trimethoprim, zidovudine, …) and alcohol consumption → among them:
    - ✓ Hydroxyurea is the most notorious → induces the largest ↑ in MCV (oval macrocytosis >110 fL).
    - ✓ a lesser degree of macrocytosis (100–110 fL) may result from use of:
      - Zidovudine & chemotherapy (oval macrocytosis), or
      - Alcohol (round macrocytosis).

Macrocytic anemia

Step 2. Rule Out Nutritional Causes of Macrocytic Anemia

- The next step is → to rule out **nutritional** causes (B12 or folate deficiency)

① it prefer to use serum homocysteine for initial screening (because of its higher sensitivity)

✓ a normal homocysteine → folate deficiency extremely unlikely

② it advocate concomitant determination of serum B12 ☞ to safeguard against Lab error in view of the dire clinical consequences associated with Vit-B12 deficiency

✓ In B12 deficiency, ↓ serum B12 ☞ ☑ B12 levels may be spuriously low during: pregnancy, in elderly patients, and in patients with low WBC counts.

- In these instances + in borderline-low B12 levels → mesurement of methylmalonic acid level

☑ If one of ① or ② tests has abnormal results ☞ serum methylmalonic acid level should be checked

③ serum methylmalonic acid level:

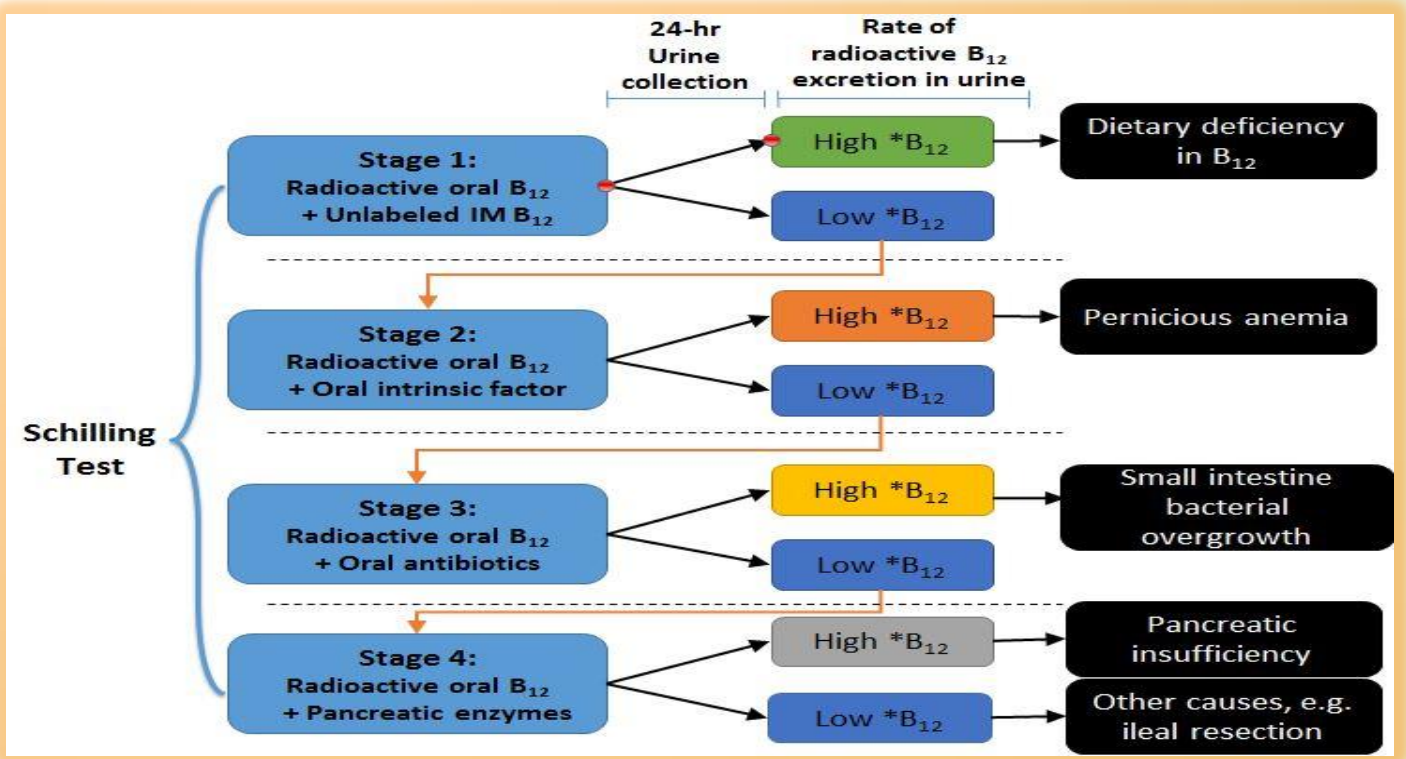
✓ an increased level → strongly suggests B12 deficiency

Macrocytic anemia

- Once vitamin B12 deficiency is confirmed ☞ the next step is to determine the cause:

1. The initial test: is to screen for the presence of IF-antibodies
   - ✓ if IF-Ab present → diagnosis of PA ⇒ additional testing may be unnecessary.
2. Otherwise, the Schilling test is performed → to differentiate PA from primary malabsorptive disorders (tropical sprue, celiac sprue, IBD, amyloidosis, and intestinal lymphoma)

IF intrinsic factor
PA: pernicious anemia
IBD: inflammatory bowel disease



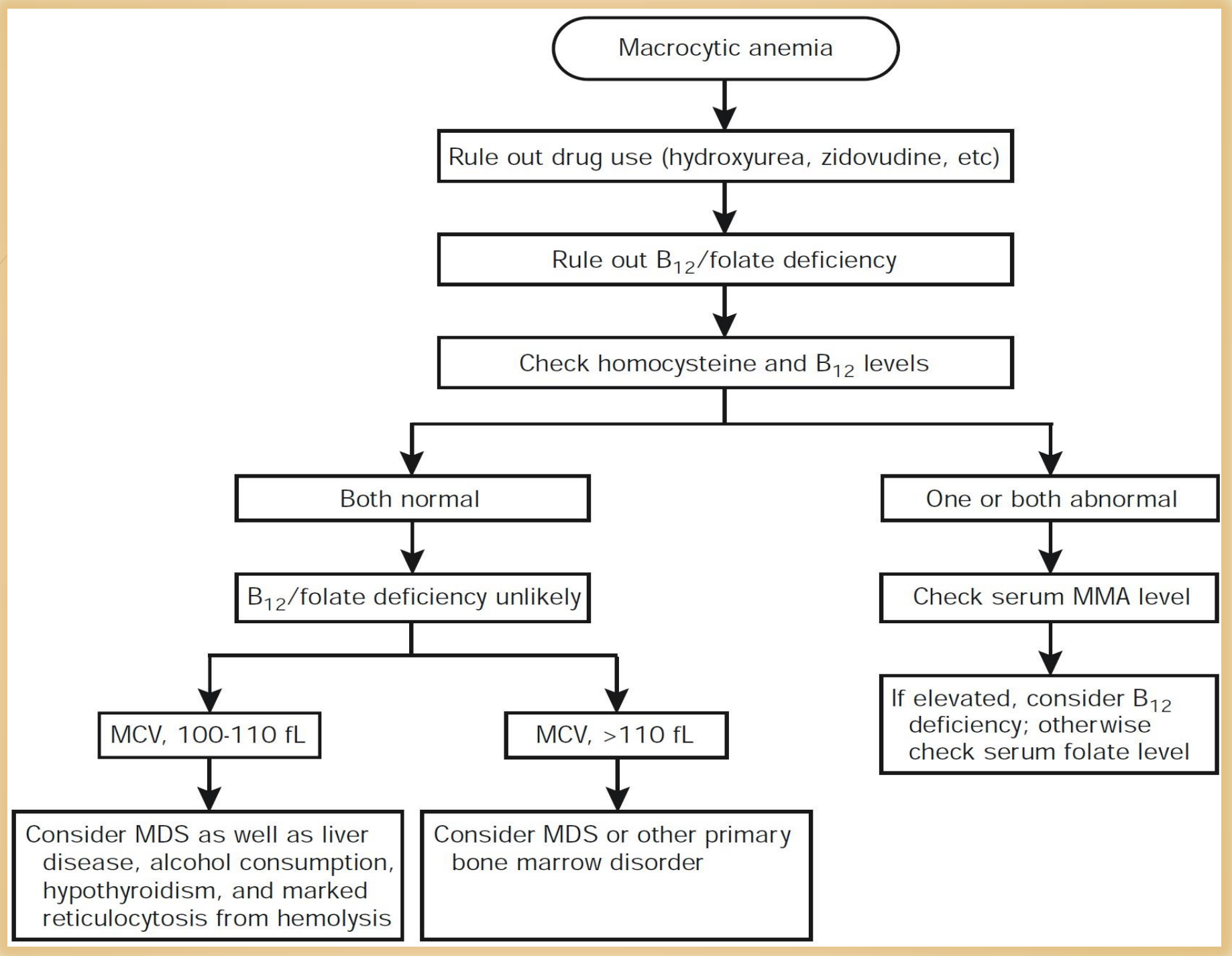
Macrocytic anemia

Step 3. Evaluating Non–Drug Induced, Non-nutritional Macrocytic Anemia

- Further investigation of these macrocytic anemia is → subcategorizing based on **MCV**:

1. Marked macrocytic anemia (MCV >110 fL)
   - ✓ almost always associated with a primary BM disease (eg, MDS, AA, PRCA, or LGL disorder) ☞ BM biopsy is indicated.
2. Mild macrocytic anemia (MCV, 100–110 fL)
   - ✓ can be associated with MDS or more benign conditions (liver disease, alcohol consumption, hypothyroidism, and marked reticulocytosis from hemolysis)
   - ✓ it is important to obtain detailed information from PBS before proceeding to BM biopsy.
     - polychromasia ☞ suggests hemolysis as the cause of macrocytosis,
     - round morphology of RBCs ☞ suggests liver disease (target cells are also evident) or hypothyroidism.

PRCA: pure red cell aplasia / **AA:** aplastic anemia / **LGL:** large granular lymphocyte


Macrocytic anemia
Rule out drug use (hydroxyurea, zidovudine, etc)
Rule out B_{12}/folate deficiency
Check homocysteine and B_{12} levels
Both normal
One or both abnormal
B_{12}/folate deficiency unlikely
Check serum MMA level
If elevated, consider B_{12} deficiency; otherwise check serum folate level
MCV, 100-110 fL
MCV, >110 fL
Consider MDS as well as liver disease, alcohol consumption, hypothyroidism, and marked reticulocytosis from hemolysis
Consider MDS or other primary bone marrow disorder

Thanks for your attention