Anemia

NABIL AL-KOURAINY, M.D.

PGY1, INTERNAL MEDICINE

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Definition

- **Deficiency in O2-carrying capacity of blood 2/2 decreased RBC mass.**
- May be due to RBC:
  - **Loss:** bleeding, sequestration
  - **Decreased production:** (hypoproliferative)
    - Defective Hgb synthesis
      - Defect in heme - iron, porphyrin ring or globin
      - Deficiency in Fe, B12, Folate
    - Impaired BM or stem cell function including any myeloid dysfunction or infiltrative process
      - Leukemia
      - Decreased EPO (fron renal failure) or decreased BM response to EPO
  - **Increased destruction:** (hemolysis)
    - SSA
    - MAQHA

Symptoms of anemia

- **Decreased oxygenation**
  - Exertional dyspnea
  - Dyspnea at rest
  - Fatigue
  - Bounding pulses
  - Lethargy, confusion
- **Decreased volume**
  - Fatigue
  - Muscle cramps
  - Postural dizziness
  - syncope

Q: A 55-year-old woman is evaluated during a routine examination. She underwent biliopancreatic diversion with duodenal switch 8 years ago for treatment of obesity-related complications and lost 68.0 kg (150.0 lb) in the first year following surgery. Her weight has been relatively stable for the last year. She has generalized fatigue, involuntary muscle movement, mostly at night, dry skin, and brittle nails. Denies changes in vision or hearing. Her other medical problems are type 2 diabetes mellitus and hypertension. Her prescription medications are metformin and lisinopril, and she also takes an over-the-counter multivitamin. Her last colonoscopy, performed 5 years ago, was normal.

On physical examination, blood pressure is 140/79 mm Hg and pulse rate is 63/min. BMI is 25. The examination is otherwise unremarkable.

Laboratory studies reveal a hemoglobin level of 10.5 g/dL (105 g/L) and a mean corpuscular volume of 85 fL.

Which of the following deficiencies best explains this patient's current findings?

a) Copper

b) Iron

c) Vitamin A

d) Vitamin B12

adapted from MKSAP 17

Key points:

- **iron deficiency commonly occurs following RY-Gastric Bypass**, Patients with iron deficiency are likely to have hypochromic, microcytic anemia and may have brittle or deformed nails, cheilitis, pica, and **restless legs syndrome**. Of note: Visual symptoms are not seen with iron deficiency anemia.

Clinical Presentation

- **Acute hemolysis**
  - Intravascular hemolysis - acute back pain, free Hgb in plasma and urine, RF
- **Moderate anemia**
  - Fatigue
  - Loss of stamina
  - Dyspnea
  - Tachycardia with exertion

Evaluation by History

Symptoms of known diseases causing anemia

- Gastric ulceration
- Rheumatoid arthritis
- Renal failure

Duration of symptoms:

- Hemoglobinopathies in longer duration Treatment history
- Medications for pain, supplementation: Fe, B12, and folate
- Nutritional history

Physical Exam

- Nourishment
- Signs of disease
- Vitals – fever, tachycardia, blood pressure
- Pallor
- Jaundice
- Lymphadenopathy
- Bone tenderness
- Petechiae
- CVS: Flow murmurs
- Resp: Dyspnea
- Abdomen: Splenomegaly

Cause(s) of Anemia	History	Physical findings
All causes		• Nail bed or palm crease pallor • Conjunctival pallor (suggests a hemoglobin < 9 mg/dl)
Iron deficiency (general)	• Pica—desire to eat unusual substances (e.g., ice, clay) • Restless legs • Sore tongue	• Glossitis • Chelitis • Koilonychia ("spoon nails")
Iron deficiency due to blood loss	• Melena, hematochezia, hematemesis • Hematuria	• Bloody stool or melena
Iron deficiency due to malabsorption	• Diarrhea • Abdominal bloating	• Dermatitis herpetiformis (in celiac disease)
Vitamin B12 deficiency	• Paresthesias • Ataxia • Memory loss, dementia • History of malabsorption or gastrectomy	• Glossitis • Chelitis • Decreased proprioception • Decreased vibratory sense
Leukemia, lymphoma	Fevers, night sweats, fatigue	• Lymphadenopathy • Splenomegaly • Purpura, ecchymoses

Note: the majority of patients seen in clinic who are diagnosed with anemia are asymptomatic

In the **acutely anemic** patient who is **volume depleted**, it is important to note that the **hemoglobin or hematocrit** may be **overestimated** **on the initial blood sample**, since these are measures of blood concentration

http://legacy.hopkinsilc.org/w/images/1/Anemia%202014/Anemia-table-history-and-physical-findings.png

Investigations:

Laboratory definition of anemia

- **Hgb**
  - **<12g/L (women)**
  - **<13g/L (men)**

most* patients will experience some symptoms related to anemia (no matter how slow the onset) when the hemoglobin level reaches ***7 g/dL.***

* However, keep in mind pt's baseline Hgb. This is why SSA pt can be asymptomatic at a Hb of 6, while you or I will be symptomatic at a Hb of 11. ***The reason for 7 as a transfusion standard is for reducing the risk of cardiac complications of hypoxemia from anemia.***

Lab Measurements (cont'd)

- **Hgb**
- **Hct**

- **RBC** = millions of RBCs per microliter of whole blood
  - A measure of the number of RBCs per volume. Low in most cases of anemia. **If elevated, consider thalassemia.**

- **MCV** = Mean corpuscular volume
  - MCV is the result of the average of RBC sizes, so a normal MCV may result from two populations of cells (i.e., small and large RBCs).
    - **If > 100 → Macrocytic anemia**
    - **If 80 – 100 → Normocytic anemia**
    - **If < 80 → Microcytic anemia**
- **RDW** = RBC distribution width
    - = (Standard deviation of red cell volume ÷ mean cell volume) × 100
    - Normal value is 11-15%
    - An elevated RDW suggests a wide range of RBC sizes; in combination with a normal MCV consider microcytic and macrocytic RBC populations.

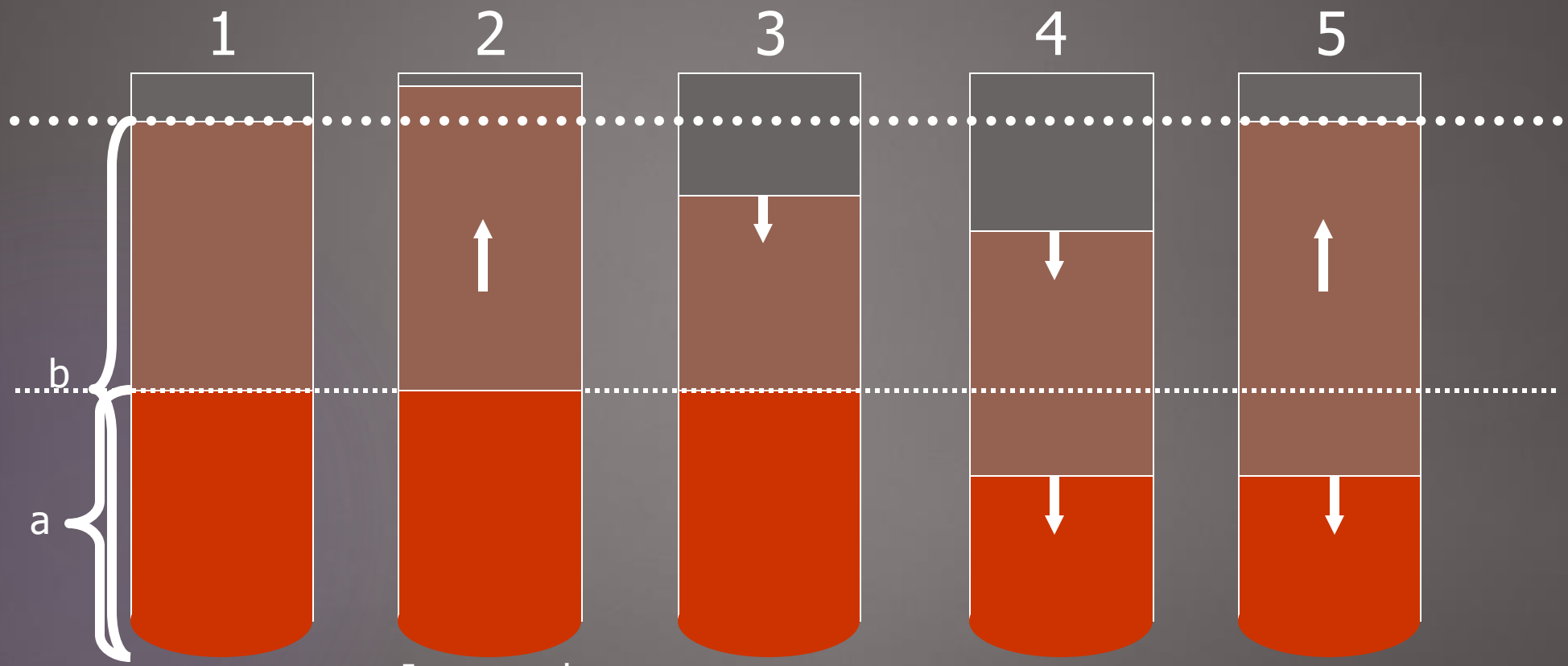
Special Considerations in Determining anemia

- **Acute Bleed**
  - Drop in Hgb or Hct may not be shown until **36 to 48 hours after acute bleed** (even though patient may be hypotensive)
- **Pregnancy**
  - In third trimester, RBC and plasma volume are expanded by 25 and 50%, respectively.
  - Labs will show **reductions in Hgb, Hct, and RBC count**, but according to RBC mass, are actually **polycythemic**
- **Volume Depletion**
  - Patient's who are severely volume depleted may not show anemia until **after rehydrated**

Symptoms of acute blood loss

- In acute blood loss **Hgb/Hct does not accurately reflect the volume of blood loss**
  - **Mild** - asymptomatic - compensation thru enhanced O2 delivery by changes in pH and increased CO2
  - **10-15%** - hypotension and decreased organ perfusion
  - **>30%** - postural hypotension, tachycardia
  - **>40%** - hypovolemic shock, confusion, diaphoresis, dyspnea

Volume changes/acute bleeding and anemia



Classification of Anemia (Adults) Teoman SOYSAL Prof. MD Definition of anemia

Corrected reticulocyte count

*Always correct for the **retic ct**. Why correct? Because men and women have diff nl Hct.*
corrected reticulocyte count = reticulocyte % x (Pt Hct/nl Hct*).
*40% women, 45% men

C-retic > 2.0% suggest **hemolysis** or **acute blood loss**. < 2.0% suggest **hypoproliferation**.

The normal reticulocyte count is 0.5-1.5%. Insufficient response (not enough) hypo. Vs, adequate response (trying to correct for loss = hemolytic)

Vocabulary of anemia

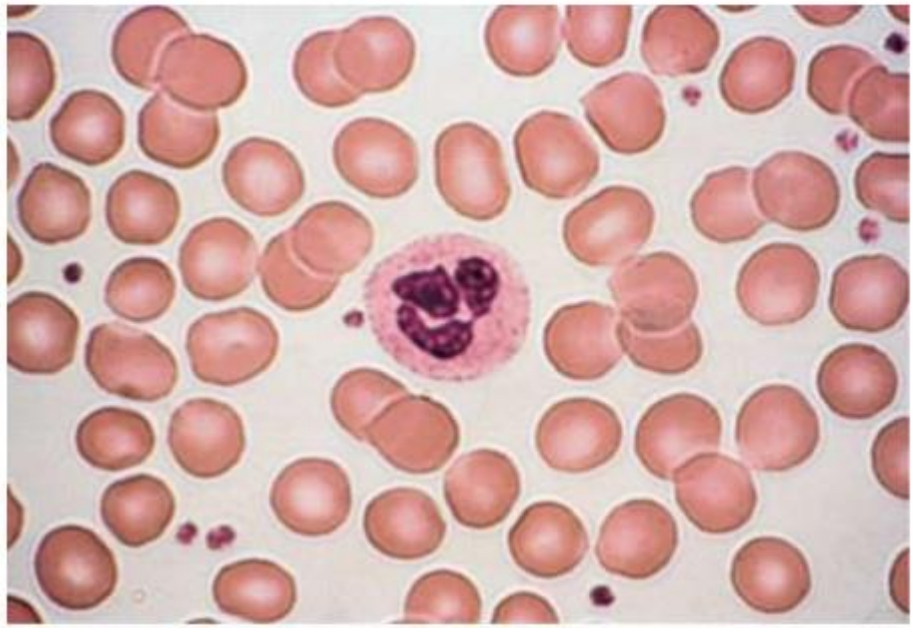
Acanthocytes	Red cell membrane defects due to chronic disease, organ failure
Agglutination	Red cells clumped together due to IgM antibodies
Anisocytosis	Variation in red cell size, often reflected in an increased red cell distribution width (RDW)
Basophilic stippling	Blue stippled appearance in mature red cells due to retained ribosomes
Bite cells/blister cells	Red cells with semicircular defects as a result of oxidized, precipitated hemoglobin
Burr cells	Red cell membrane defect characterized by irregular borders associated with renal or hepatic disease
Howell-Jolly Bodies	Large red cell inclusion that is a nuclear remnant, associated with absent splenic function
Hypochromia	Increased central pallor, associated with restricted hemoglobin production due to iron deficiency or thalassemia
Macrocytes	Large red blood cells
Microcytes	Small red blood cells
Pappenheimer bodies	Small red cell inclusions indicative of alcohol use or post-splenectomy state
Poikilocytosis	Variation in red blood cell shape
Polychromasia	Blue cast to red cells indicating their recent emergence from the bone marrow
Rouleaux	Red cells stacked together like coins, due to high protein/paraprotein
Schistocytes	Fragmented red cells due to intravascular hemolytic processes
Spherocytes	Round red cells lacking central pallor due to reduced red cell membrane
Spur cells	Red cell membrane defect characterized by irregular spines associated with severe liver disease
Target cells	Red cell membrane defect associated with thalassemia or liver disease
Tear drops	Red cells in the shape of teardrops, observed in myelophthistic processes, liver disease

http://legacy.hopkinsilc.org/w/images/1/Anemia%202014/Anemia-table-vocabulary.png

Peripheral smears

- Cell size
- Hb content
- Anisocytosis
- Poikilocytosis
- Polychromasia

- Gives clues to specific disorders

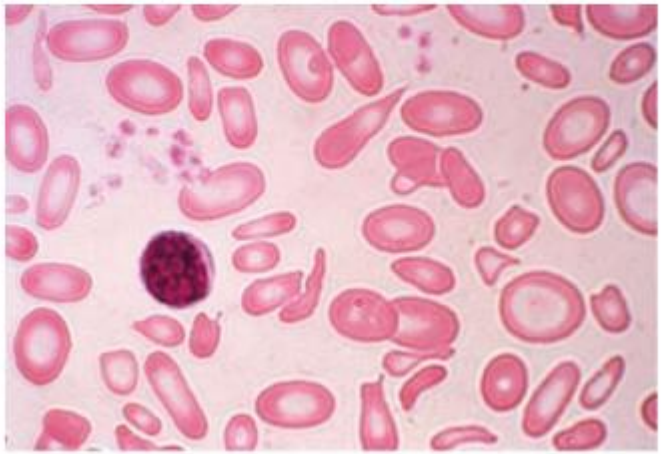


Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

Normal peripheral smear

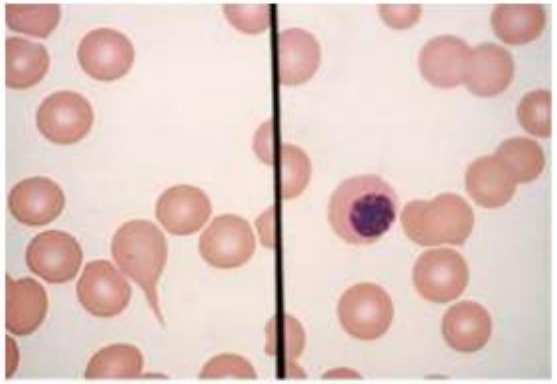
Let's go through some common examples.

***note this is not comprehensive**



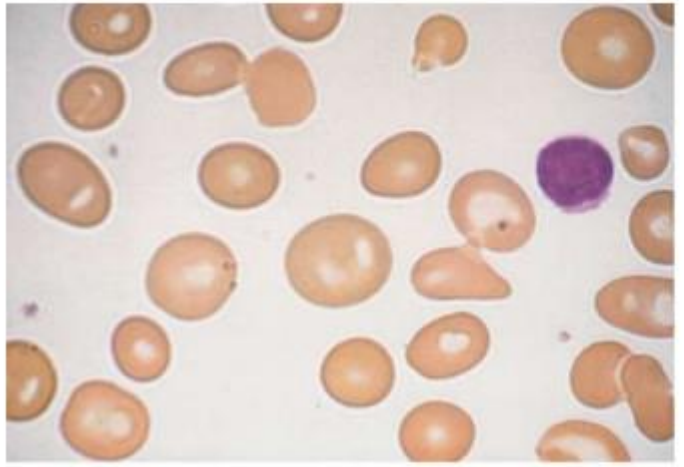
Severe Iron defeciency anemia

Anisocytosis (size), Poikilocytosis (shape)



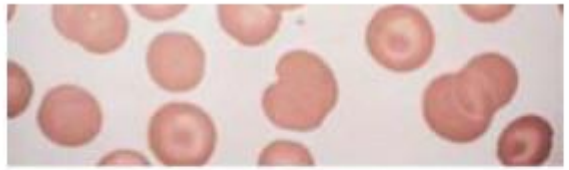
Myelofibrosis

Tear drop shaped cells, nucleated cells



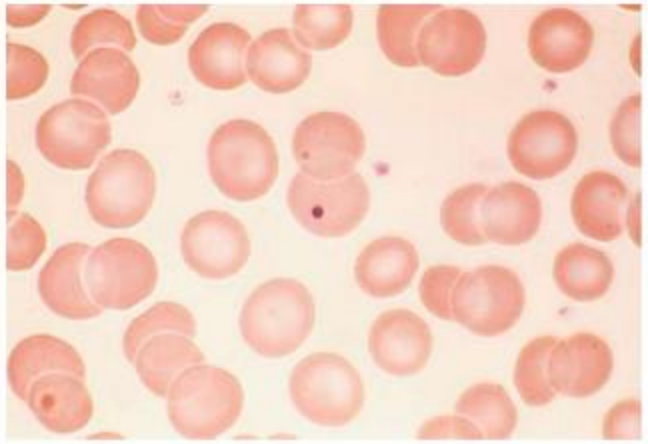
Macrocytosis

Macrocytes, Ovalocytes



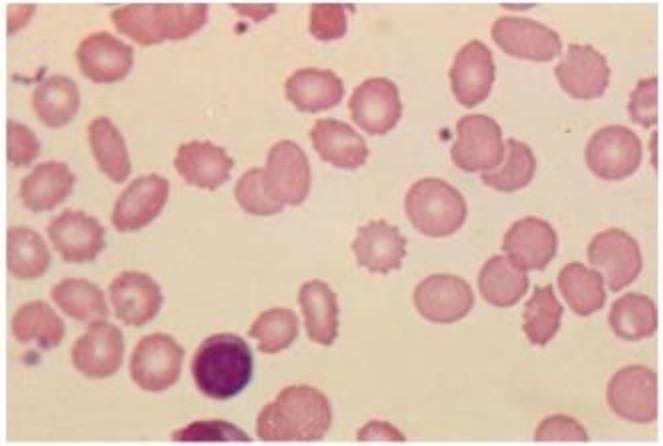
Thallassemia

Target cells



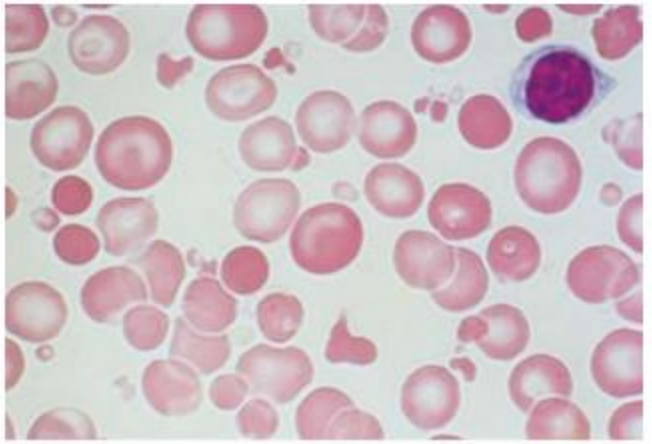
Howell–Jolly bodies

Seen with: post-splenectomy or congenital absence of spleen as well as: amyloidosis, severe HA, megaloblastic anemia, hereditary spherocytosis, and MDS. Can also can be seen in premature infants.



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

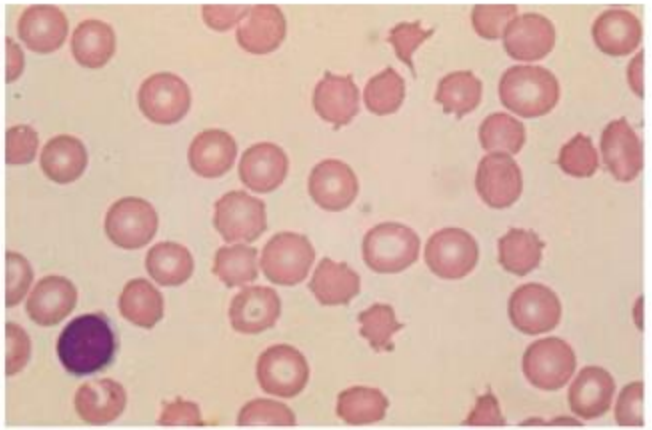
Uremia



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

Red cell fragmentation

Aka schistocytes – seen in intravascular hemolysis as seen in sepsis



Source: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine, 18th Edition*: www.accessmedicine.com

Spur cells

Aka Burr cells are RBC membrane defect characterized by irregular spines - associated w ith sev ere liver disease

Fe studies

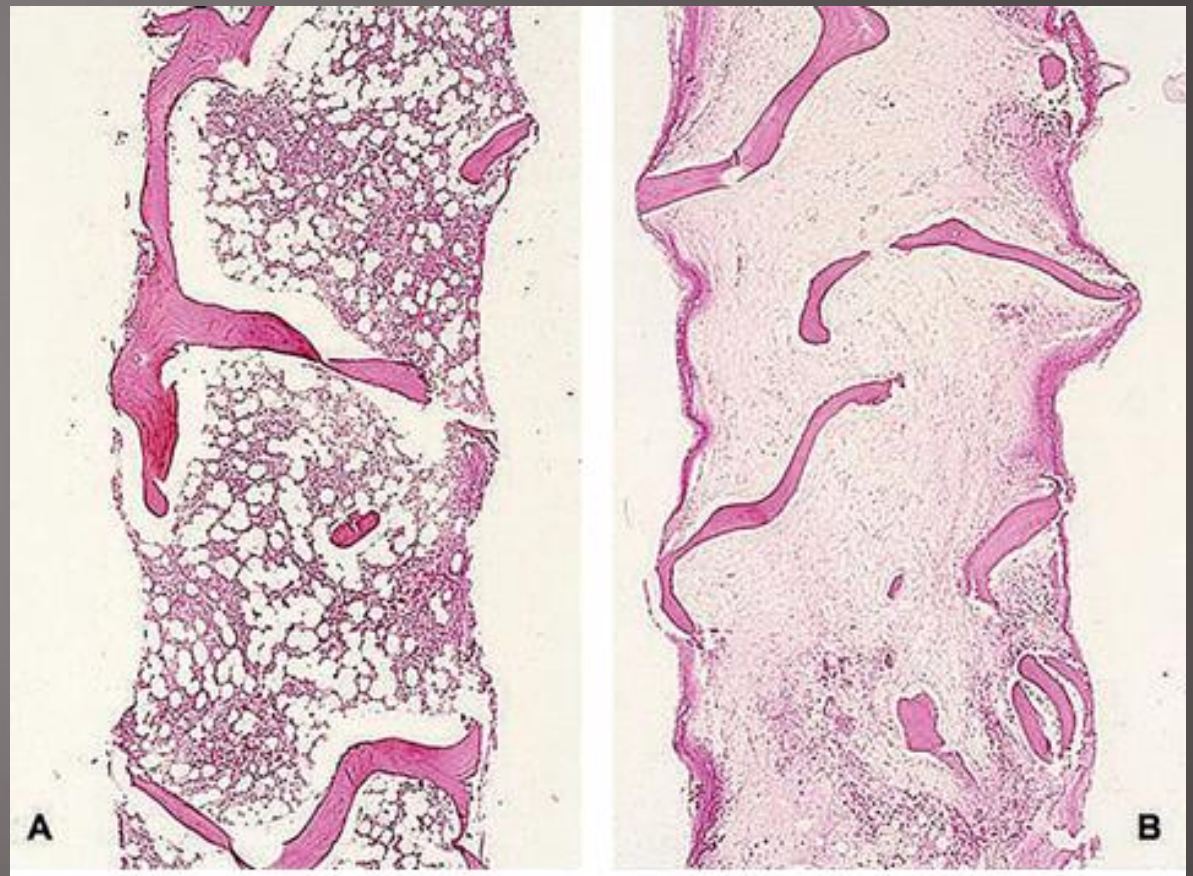
- Serum Iron: 50–150 µg/dL
- TIBC: 300–360 µg/dL
- Serum ferritin (also an acute phase reactant)
  - 15-20 µg/dL – Lack of Iron stores
  - Women: ~30 µg/dL
  - Men: ~ 100 µg/dL
  - 200 µg/dL – adequate iron stores
  - Serum Transferrin saturation: 25-50%

Ferritin is most important study for Fe deficiency. Serum iron does not tell us much as it can change acutely. Similarly, a diabetic can have a normal serum glucose at any given point.

Can obtain a **soluble transferrin receptor** if ferritin is normal.

Bone Marrow Evaluation

- Mandatory in patients with **normal Fe status with hypoproliferative anemia**
  - Can be used to diagnose primary bone marrow diseases: myelofibrosis, infiltrative diseases



Source: H. Franklin Bunn, Jon C. Aster: Pathophysiology of Blood Disorders
www.accessmedicine.com

Q: A 52-year-old male presents to you with several months of fatigue. You order blood work, which shows the following:

Hemoglobin	6.9g/dL (normal 12-15g/dL)
Hematocrit	20% (normal 41-46%)
MCV	98fl (normal 80-100fl)
Reticulocyte count	3% (normal 0.5-1.5%)
Corrected reticulocyte count	1.3%
White blood count	5,500 (normal 4500-11000)
Platelets	130,000 (normal 150-350,000)

Of the causes listed, the most likely cause of this patient's anemia is:

- a) Autoimmune hemolytic anemia
- b) Glucose-6-phosphate dehydrogenase deficiency
- c) Thrombotic thrombocytopenic purpura
- d) Vitamin B12 deficiency

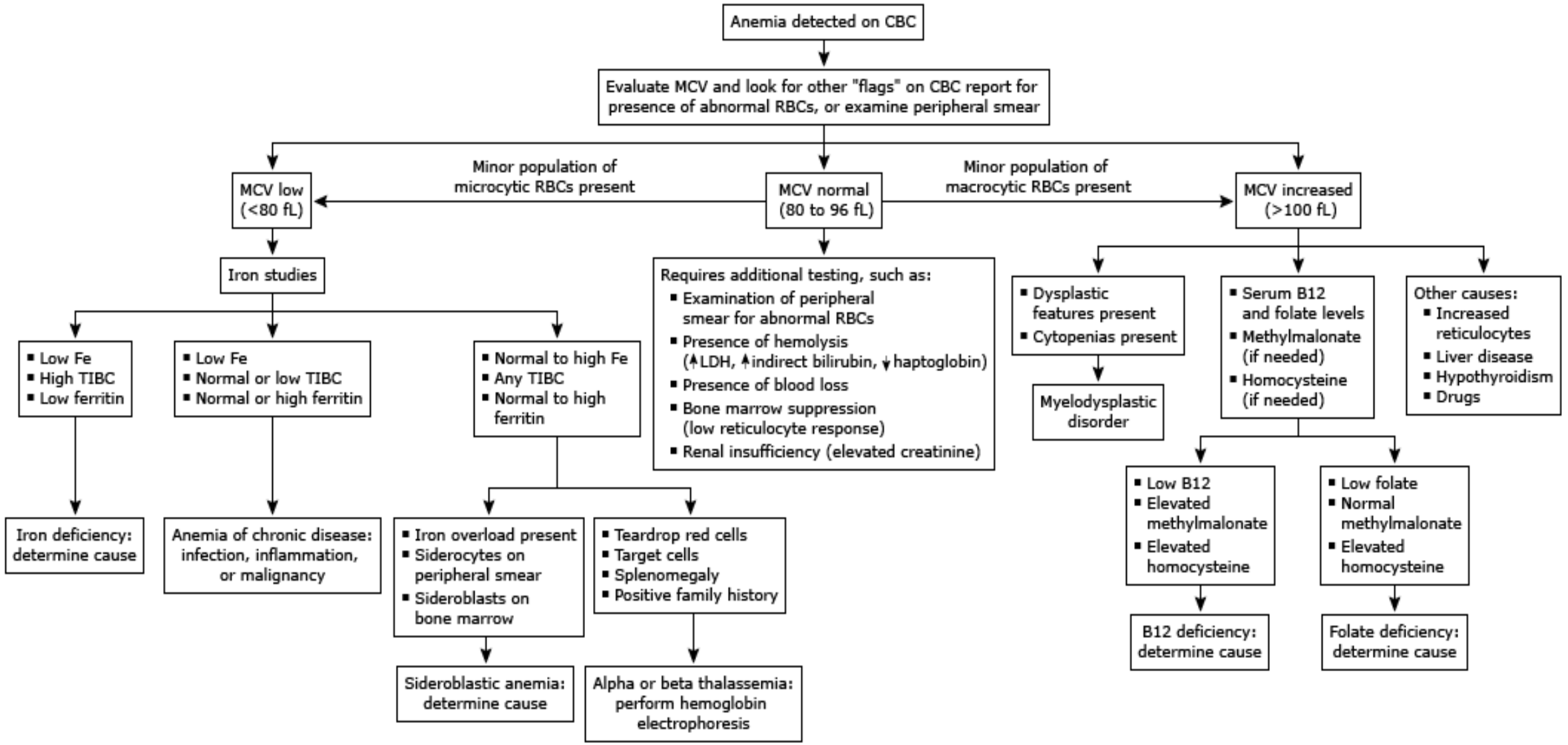
Key points:

- Low HCT with slight elevation in retic ct
  - Corrected retic ct = 1.3 %
    - (3% x 20%/45% = 1.3%)
  - **Hypo**proliferative -> *underproduction* vs all other answer choices which are hemolytic -> *destruction*

https://ilc.peaconline.org/m/1308

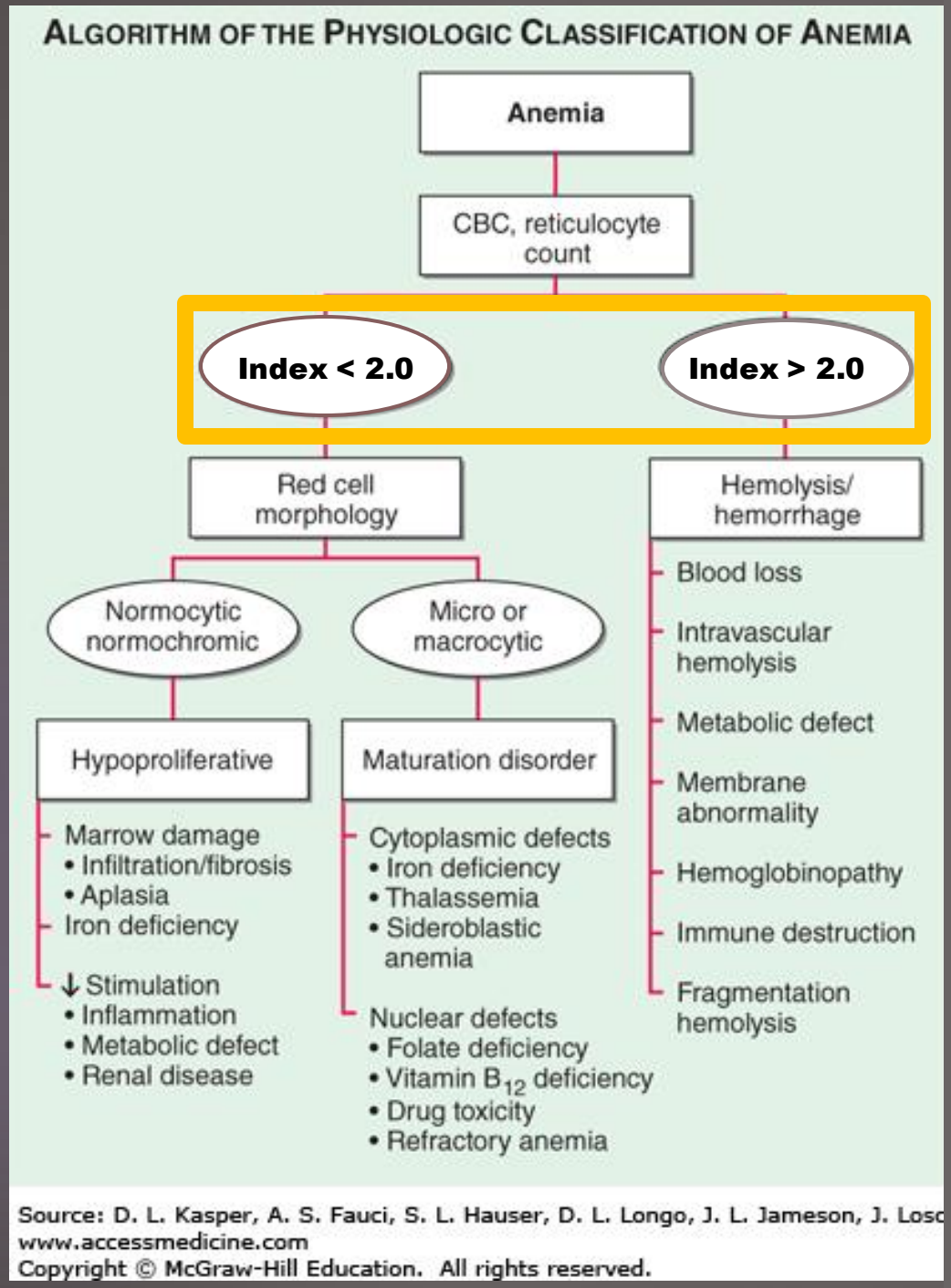
Evaluation of anemia in the adult according to the mean corpuscular volume

The MCV approach…



CBC: complete blood count; MCV: mean corpuscular volume; RBCs: red blood cells; Fe: iron; TIBC: total iron-binding capacity (transferrin); LDH: lactate dehydrogenase.

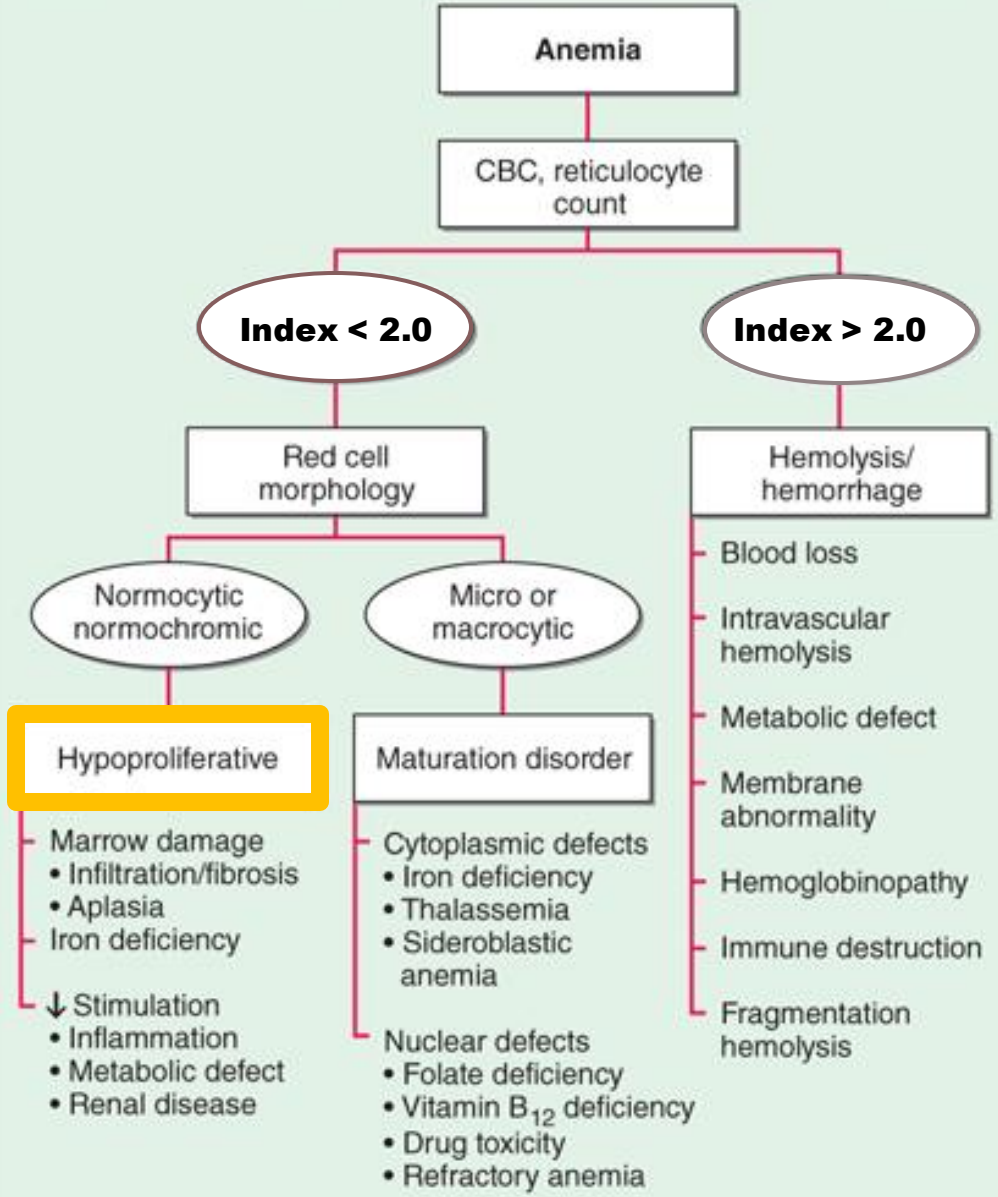
The CRC approach



1. Establish presence of anemia
2. Correct for reticulocyte count
   - < 2.0 ***hypoproliferative***
   - > 2.0 ***hemolytic or hemorrhage***

- Vast majority will be normocytic 2/2 IDA
- Question then is why are the Fe deficient?
  - Depends on age
  - **Be mindful of Red flag symptoms.**
    - 1) rectal bleeding, 2) iron-deficiency anemia (IDA), 3) weight loss, 4) family history of colon cancer, 5) fever, and 6) age of onset after age 50.
      - **Make sure cancer screening is UTD, especially CRC in patients greater than 50y.**

Algorithm of the Physiologic Classification of Anemia



Source: D. L. Kasper, A. S. Fauci, S. L. Hauser, D. L. Longo, J. L. Jameson, J. Loscalzo: Harrison's Principles of Internal Medicine, 19th Edition.
www.accessmedicine.com

Hypoproliferative anemias

- 75% of all anemias – **IDA is the most-common-cause**
- Reflects total or relative BM failure
- Causes include:
  - Inflammation
  - Ineffective EPO production due to
    - Renal dysfunction
    - T2DM
    - Hypothyroidism
  - BM damage

Work-up

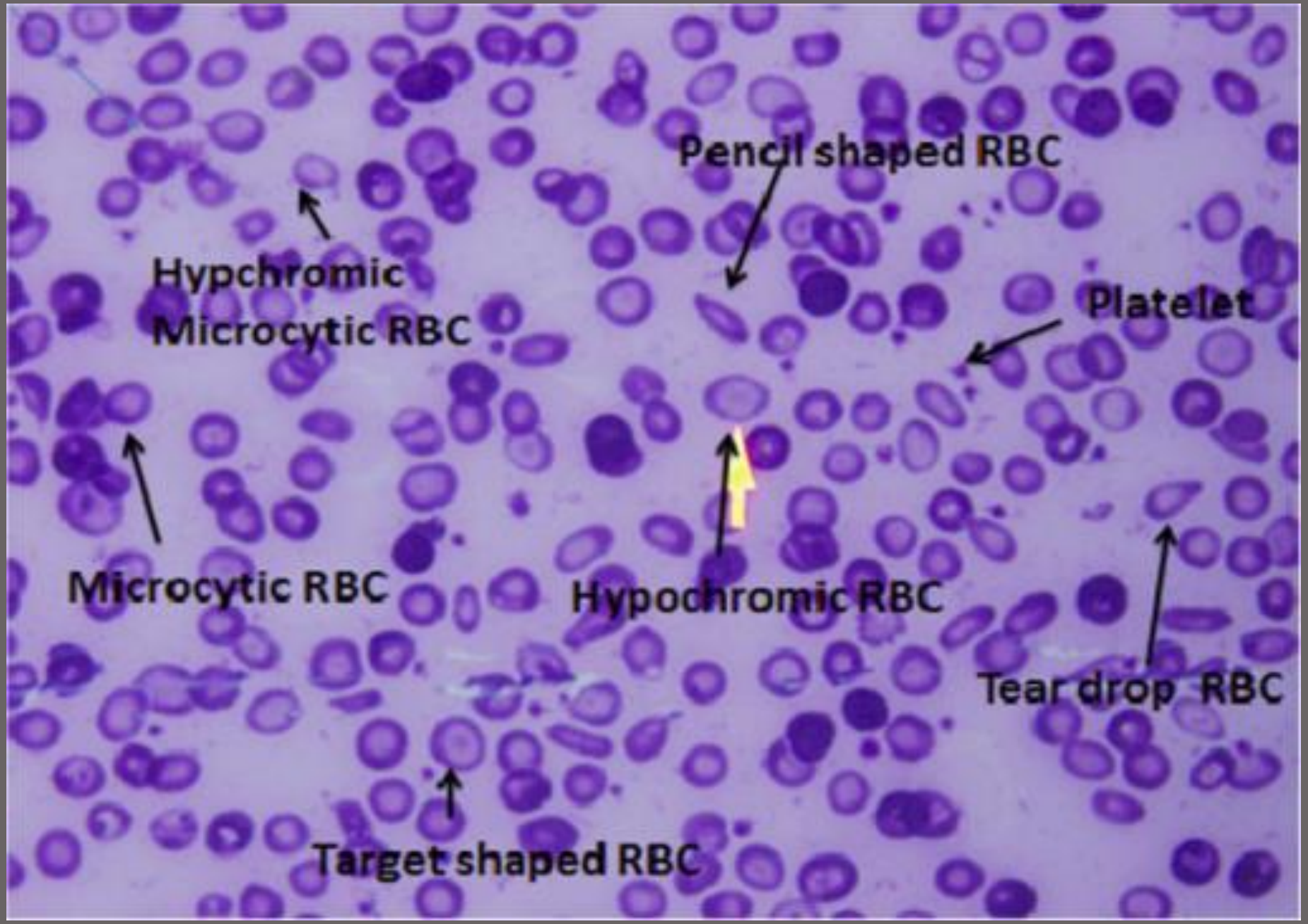
- Fe studies
- Ferritin
- Bone Marrow biopsy/aspiration

Findings: AOCD vs IDA

- AOCD:
  - Fe : Low
  - TIBC: normal or low
  - Soluble Transferrin Receptor (sTFR): Normal
  - **Ferritin: Normal – High**
- IDA
  - Fe : Low
  - TIBC: High
  - Soluble Transferrin Receptor (sTFR): High
  - **Ferritin: Low**

- Ferritin is an *acute phase reactant*. infectious processes may cause ferritin to rise, even in the presence of Fe deficiency.
- However, **in true Fe deficiency, ferritin <100ng/mL.**
  - **a ferritin >100ng/mL excludes iron deficiency** as a cause of microcytic anemia.
- transferrin assay -> elevated in iron deficiency, vs normal in AOCD

Peripheral blood film with changes attributed **to iron deficiency anemia.**



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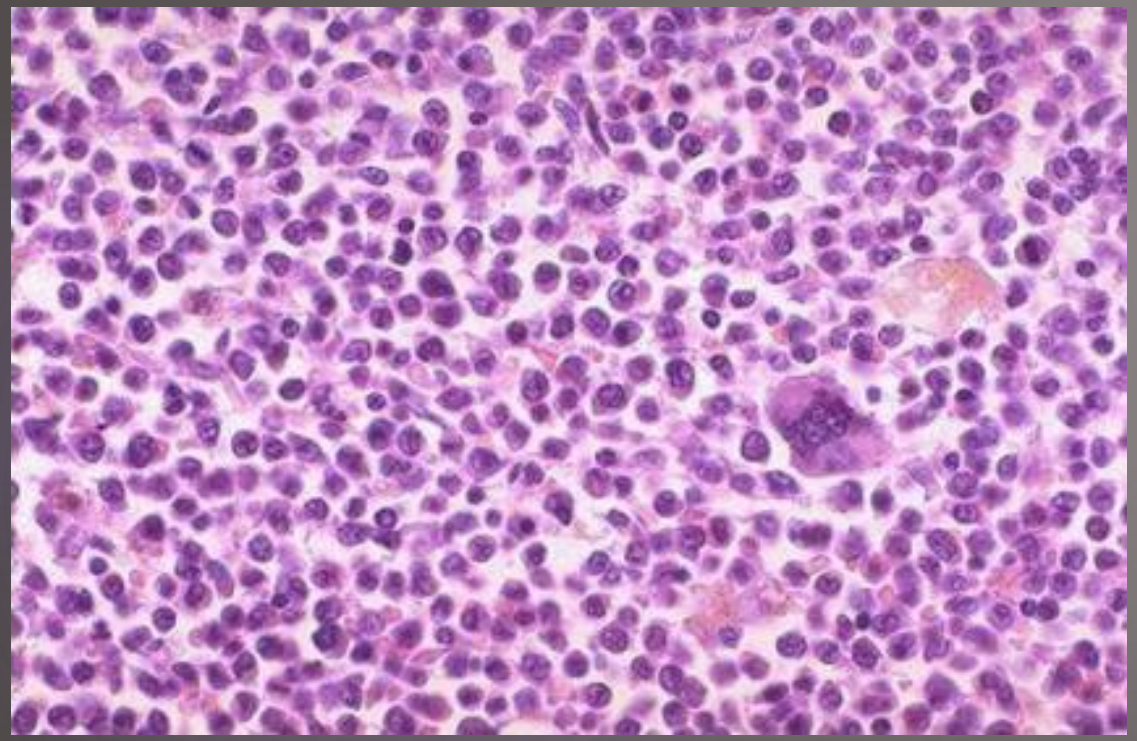
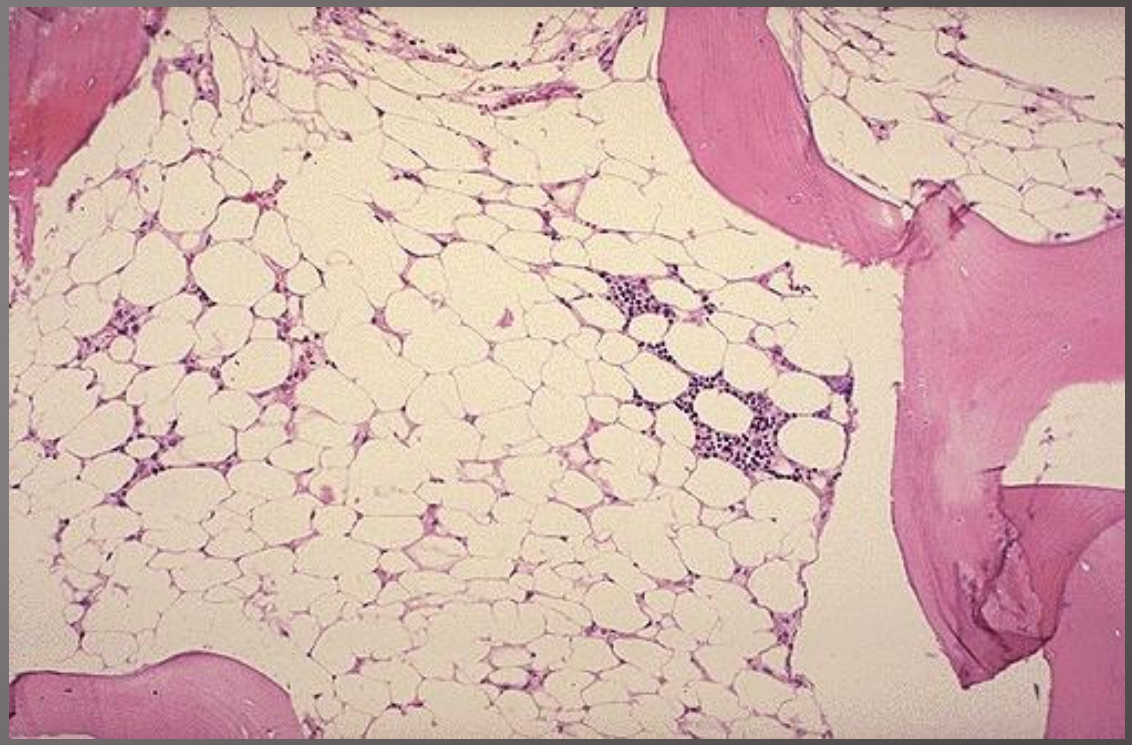
Leukemia, Lymphoma and BM aplasia



Acute myelogenous leukemia - there is one lone megakaryocyte at the right-center

https://library.med.utah.edu/WebPath/HEMEHTML/HEME031.html



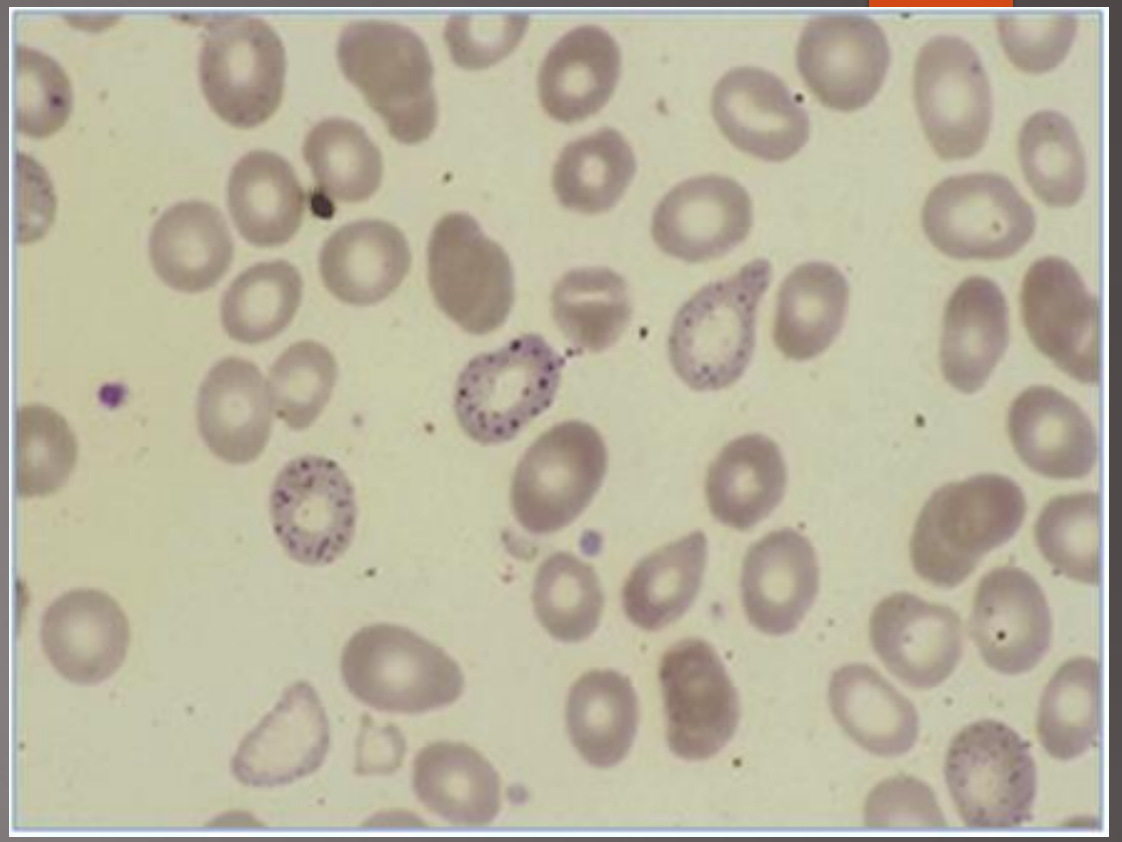
Aplastic anemia

https://upload.wikimedia.org/wikipedia/commons/3/31/Aplastic_Anemia.jpg

Q: A 52-year-old male presents to you with several months of fatigue. You order blood work, which shows the following:

Hemoglobin	11.7g/dL (normal 12-15g/dL)
Hematocrit	35% (normal 41-46%)
MCV	78.4fl (normal 80-100fl)
Reticulocyte count	1.5% (normal 0.5-1.5%)
WBC	8200 (normal 4500-11000)
Platelets	208,000 (normal 150-350,000)
Iron	185mcg/ml (normal 40-80mcg/ml)
TIBC	253mg/dl (normal 250-450mg/dl)
% iron saturation	72% (normal 20-55%)
Ferritin	400ng/ml (normal 10-300ng/ml)

Peripheral smear shows:



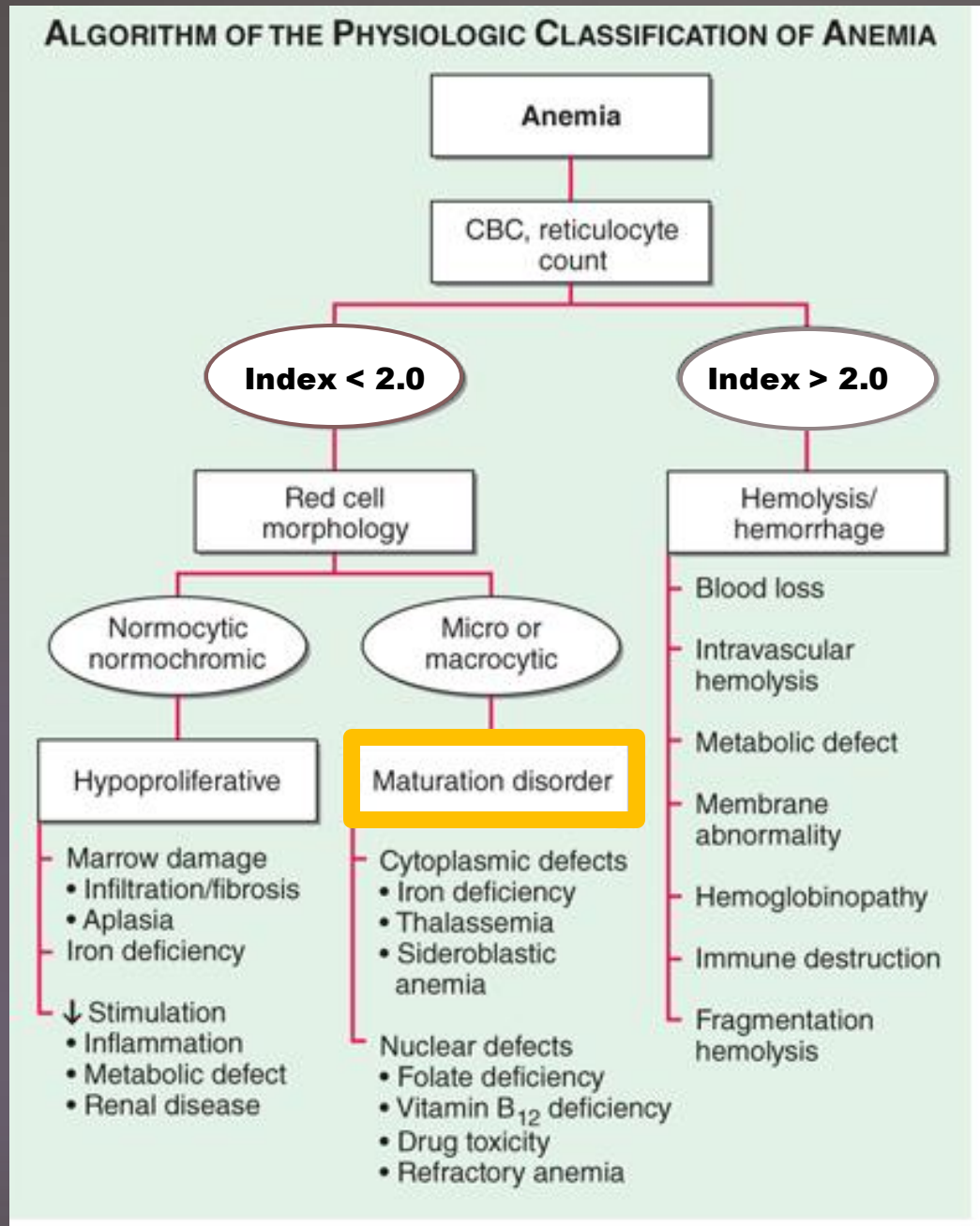
What test should be done next in order to make the diagnosis?

a) Lead level
b) Bone marrow biopsy
c) Tissue transglutaminase antibody level
d) Colonoscopy

Key points:

- **Colicky abd pain with microcytic anemia**
- Fe studies not c/w IDA or AOD
- **Basophilic stippling** seen in lead poisoning, thalassemias and other hemoglobinopathies

http://legacy.hopkinsilc.org/w/images/1/Anemia%202012/Anemia-figure-lead-2.png



Adapted from Harrison's 19th edition

Maturation disorders

- CRC <2.0
- Two types:
  - Macrocytic – nuclear abnormalities
  - Microcytic – cytoplasmic abnormalities
- Poor erythropoiesis 2/2 marrow destruction
  - BM shows erythroid hyperplasia

Nuclear maturation disorders

- B 12 deficiency
- Folate deficiency
- Toxins (MTX)
- Alcohol - > folate deficiency

Cytoplasmic maturation disorders

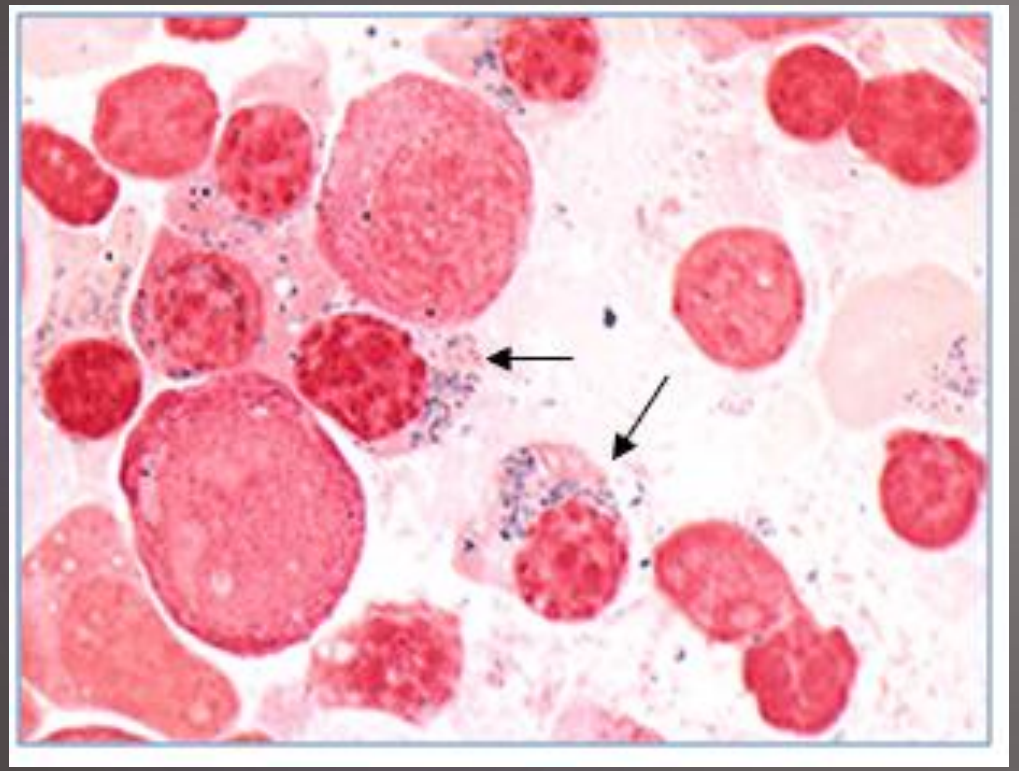
- Severe Fe deficiency
- Thalassemias
- Siderblastic

	Iron Deficiency	Thalassemia Trait
RBC count	Low	Normal or high
MCV	Low	Lower than with iron deficiency
RDW	High	Normal
Ferritin	Low	Normal or High
Peripheral smear	Microcytic, hypochromic usually with anisocytosis	Uniformly microcytic cells with occasional target cells
Bone marrow	Absent iron	Normal iron

https://ilc.peaconline.org/sites/ilc.peaconline.org/files/modules/2017/Anemia/Anemia-table-thalassemia-vs-iron-deficiency.png

Sideroblastic anemia

- relative iron overload with ineffective heme synthesis
- BM stained with Prussian blue reveals characteristic **ringed sideroblasts**



Arrows point to two examples of ringed sideroblasts

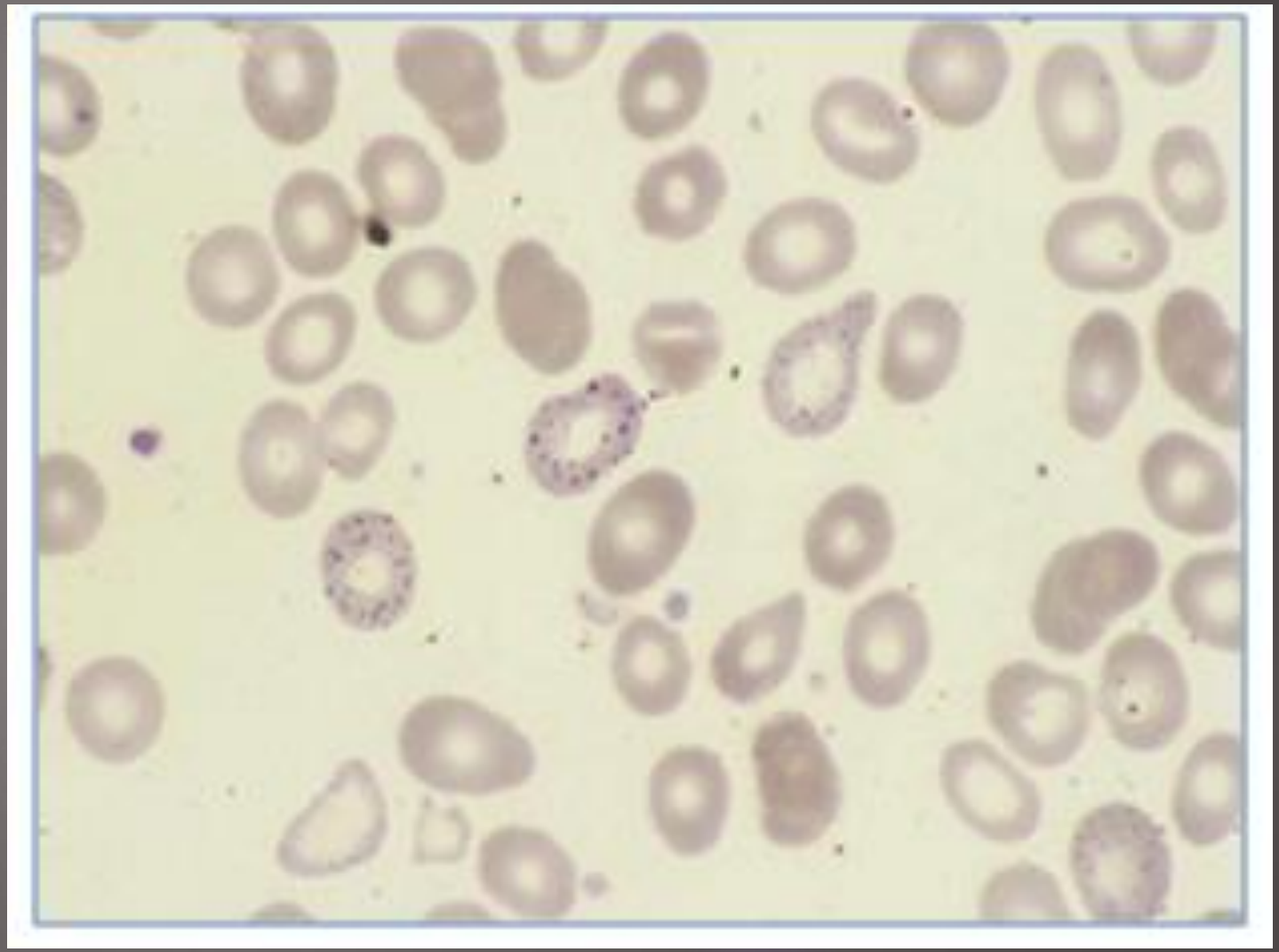
https://ilc.peaconline.org/sites/ilc.peaconline.org/files/modules/2017/Anemia/Anemia-figure-ringed-sideroblast.png

Cause	Examples/Comments
Drugs	• Isoniazid • Chloramphenicol • Linezolid
Toxins	• Alcohol • Zinc • Lead
Nutritional deficiencies	• Copper • Pyridoxine
Myelodysplastic syndrome (MDS)	• Refractory anemia with ringed sideroblasts • Usually affects platelets and white cells as well
Hereditary autosomal or X-linked sideroblastic anemia	• Rare disorders usually presenting in childhood
Hypothermia	

https://ilc.peaconline.org/sites/ilc.peaconline.org/files/modules/2017/Anemia/Anemia-table-causes-of-acquired-sideroblastic-anemia.png

Lead poisoning

- Microcytic
- motor neuropathy and abdominal pain
- basophilic stippling on PBS



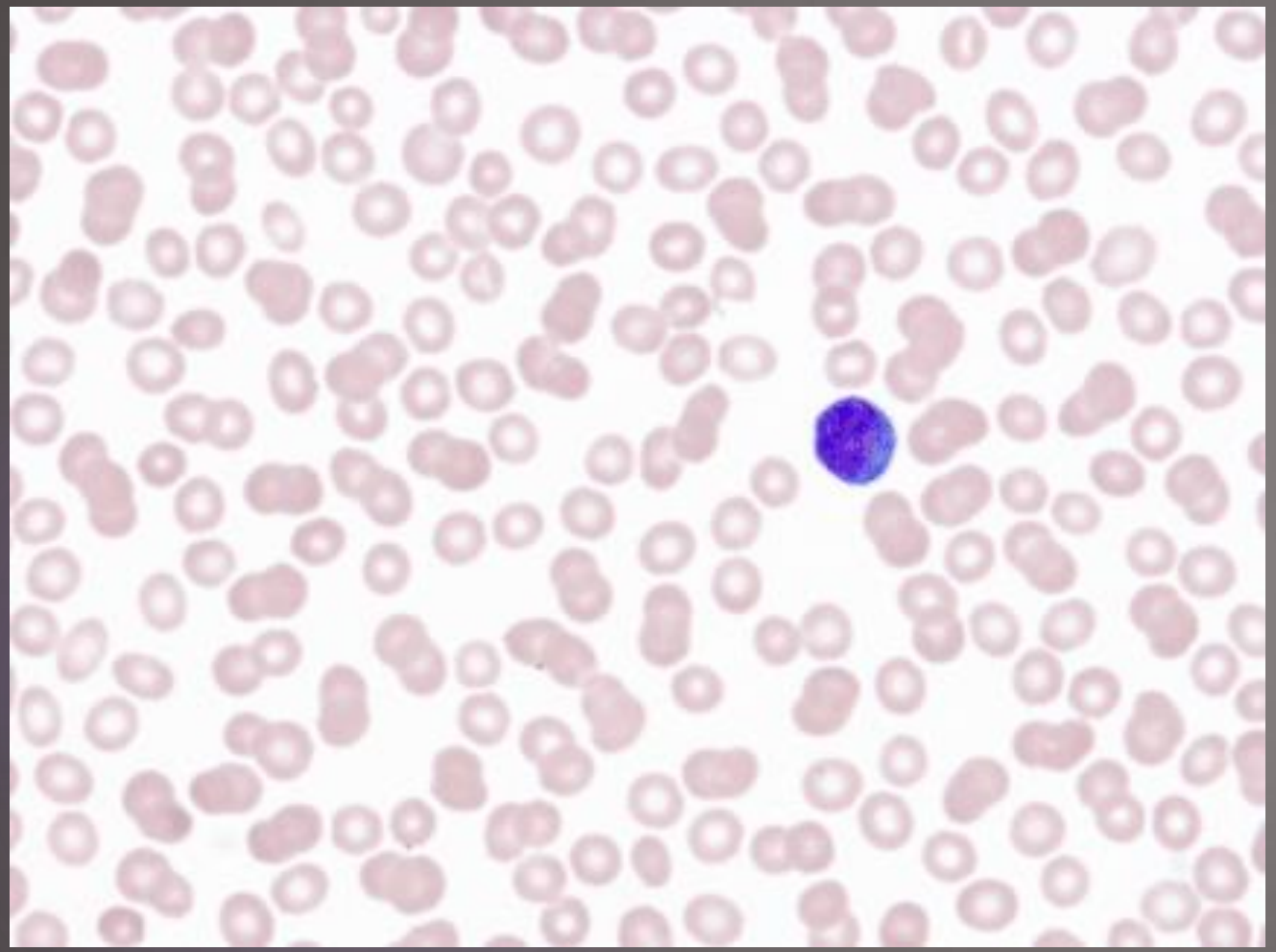
http://legacy.hopkinsilc.org/w/images/1/Anemia%202012/Anemia-figure-lead-2.png

Testing to evaluate hypoproliferative microcytic anemia

Test	Comments
Iron studies	• **Iron deficiency**: Serum iron/transferrin saturation low • **Anemia of chronic disease**: Serum iron/transferrin saturation, transferrin, TIBC low • **Sideroblastic anemia**: Serum iron elevated
Ferritin	• **Iron deficiency**: Ferritin is low • **Anemia of chronic disease**: Ferritin is normal or elevated • **Sideroblastic anemia**: Ferritin is elevated
Soluble transferrin receptor	• **Iron deficiency**: elevated • **Anemia of chronic disease**: normal
Hemoglobin electrophoresis	• **Alpha thalassemia**: normal • **Beta thalassemia trait**: hemoglobin A2 elevated; hemoglobin F increased
Lead level	• Consider with history of exposure or consistent clinical picture • Consider as cause of sideroblastic anemia

https://ilc.peaconline.org/sites/ilc.peaconline.org/files/modules/2017/Anemia/Anemia-table-tests-in-microcytic-anemia.png

Q: You are evaluating a 43-year-old male patient with normocytic anemia (hematocrit 31%; MCV 86fl). Renal function is normal, thyroid testing is normal, and there is no evidence of anemia of chronic disease. Peripheral blood smear is as follows:



Which of the following statements is true?

a) This patient most likely has myelodysplastic syndrome.

b) This patient most likely has multiple myeloma.

c) HIV infection is a potential cause of this patient's anemia.

d) Systemic lupus erythematosus is a potential cause of this patient's anemia.

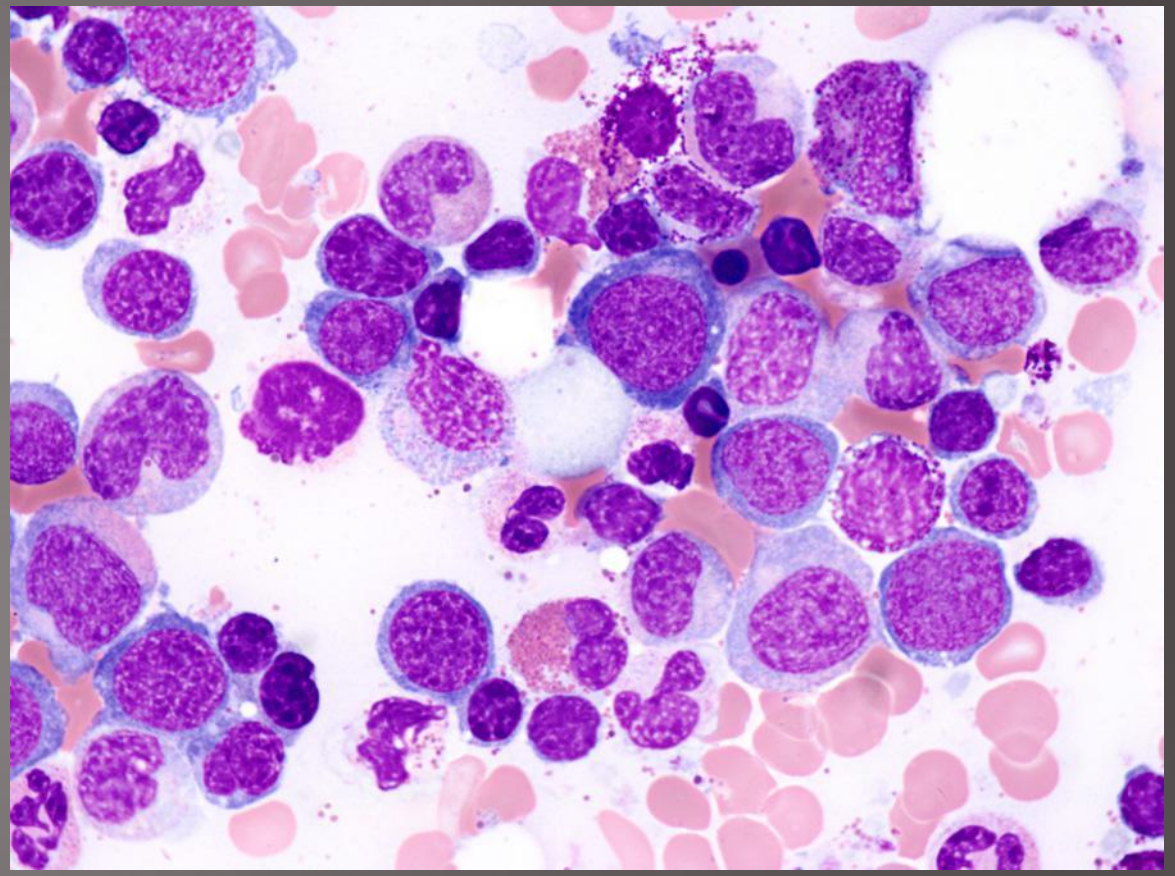
Key points

- aplastic anemia with pancytopenia
- absence of platelets
- Leukopenia
- lack of immature RBCs
- HIV infection is a possible cause of aplastic anemia.

https://ilc.peaconline.org/m/1308

Myelodysplasia

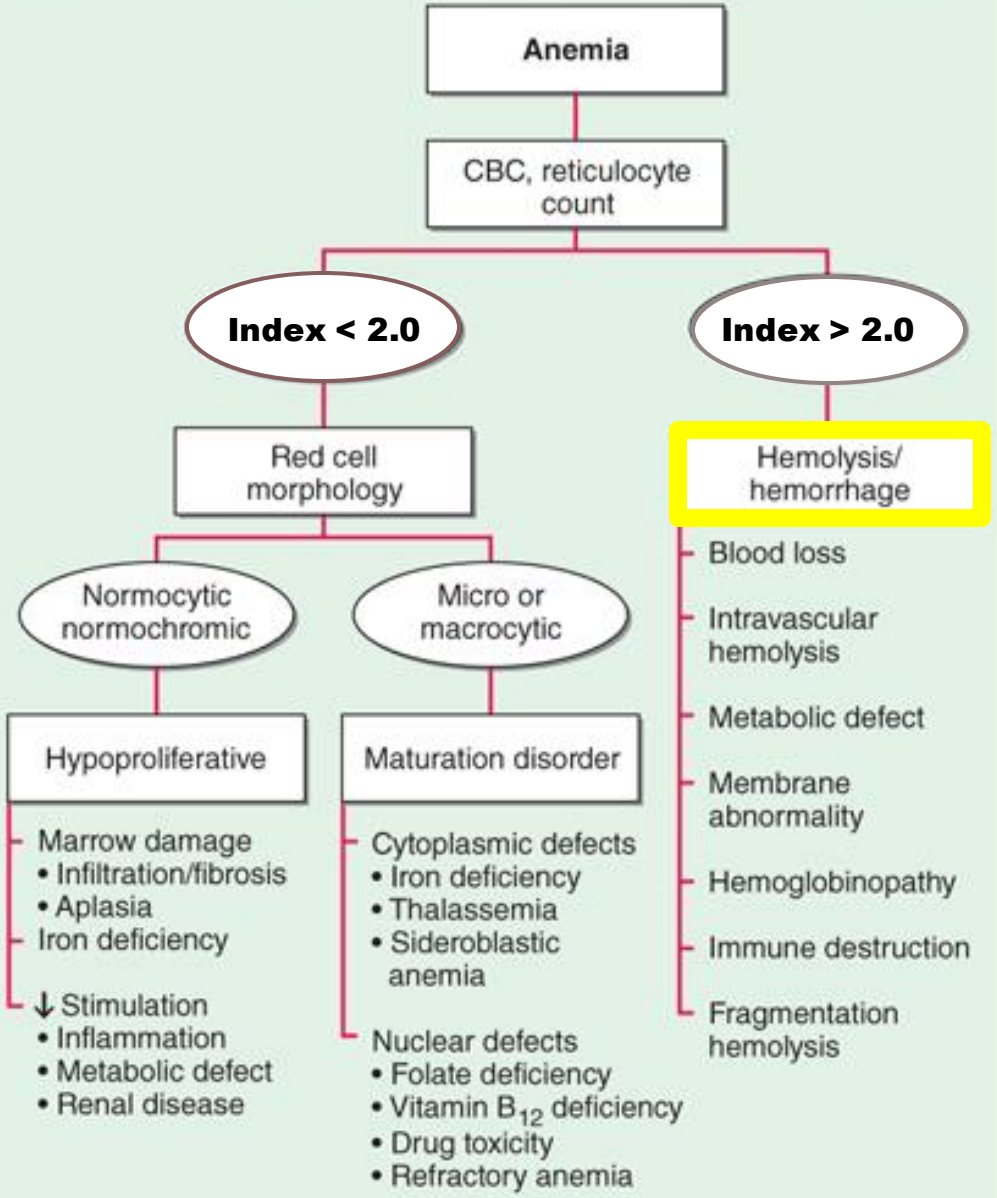
- Features:
  - Macro or microcytosis
  - Iron ring in mitochondria
  - Fe studies can be used to help differentiate from other disorders



Bone marrow aspirate – MDS with excess blasts-2 (MDS-EB2). myeloblasts are smaller, with scant pale cytoplasm.

https://img.medscapestatic.com/pi/meds/ckb/78/13278tn.jpg

ALGORITHM OF THE PHYSIOLOGIC CLASSIFICATION OF ANEMIA



Source: D. L. Kasper, A. S. Fauci, S. L. Hauser, D. L. Longo, J. L. Jameson, J. Loscalzo: Harrison's Principles of Internal Medicine, 19th Edition.
www.accessmedicine.com

Adapted from Harrison's 19th edition

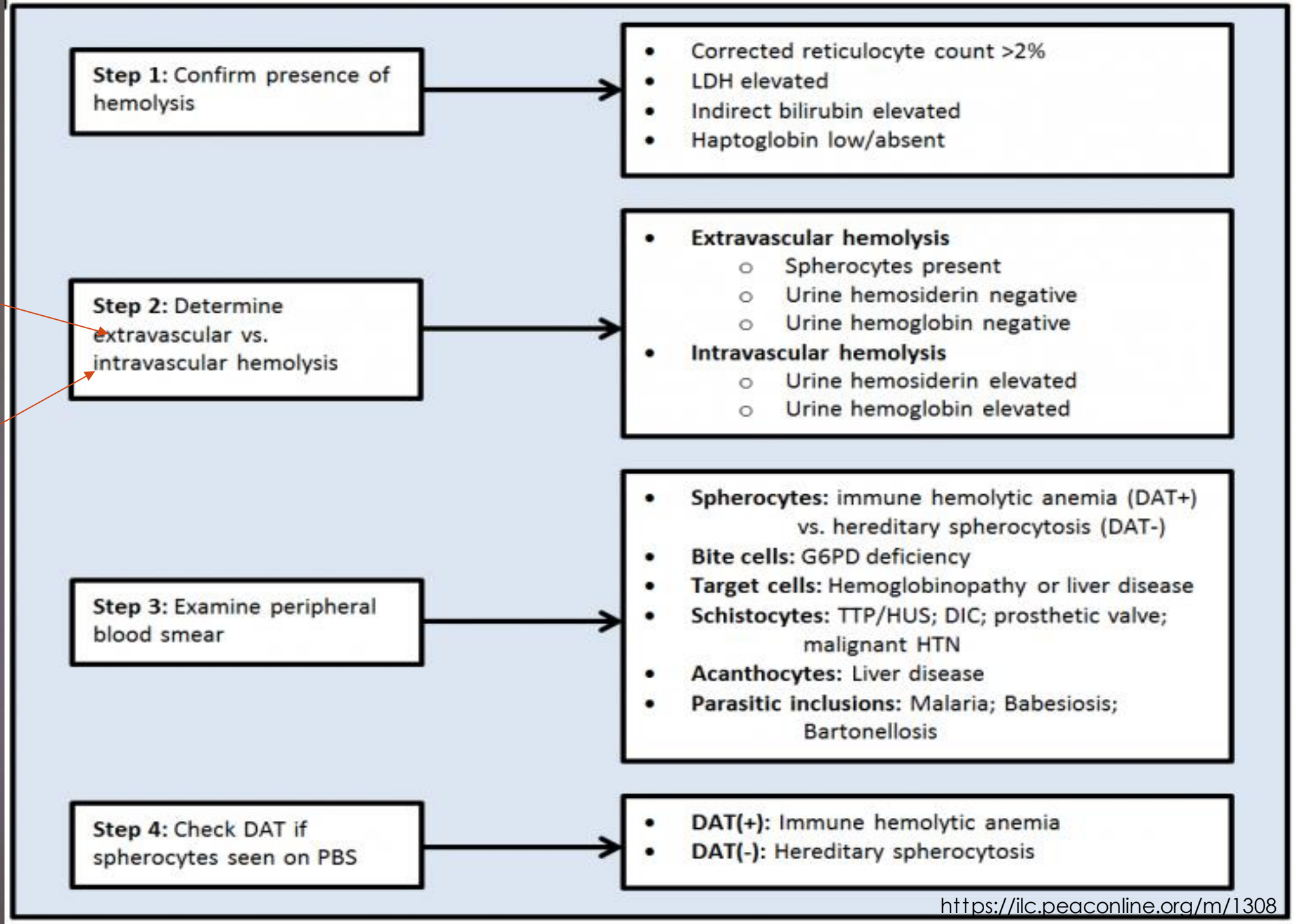
Acute blood loss

- cRetic > 2.0
- Symptoms:
  - In acute blood loss **Hgb/Hct does not accurately reflect the volume of blood loss**
    - **Mild** - asymptomatic - compensation thru enhanced O2 delivery by changes in pH and increased CO2
    - **10-15%** - hypotension and decreased organ perfusion
    - **>30%** - postural hypotension, tachycardia
    - **>40%** - hypovolemic shock, confusion, diaphoresis, dyspnea
- Not associated with increased erythrocytosis 2/2 time required for EPO production

Evaluation of **Hemolytic Anemia**

RBCs prematurely removed from circulation by liver and spleen. Majority of cases of HA.

RBCs lyse within circulation



https://ilc.peaconline.org/m/1308

References

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