Anemia work-up

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I have nothing to disclose

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Objectives

- Different etiology of anemia.
- Mechanistic classification of anemia.
- What first line tests are appropriate for anemia work-up
- Interpretation of test and additional testing if necessary
- Understand the different causes of anemia and how they may present

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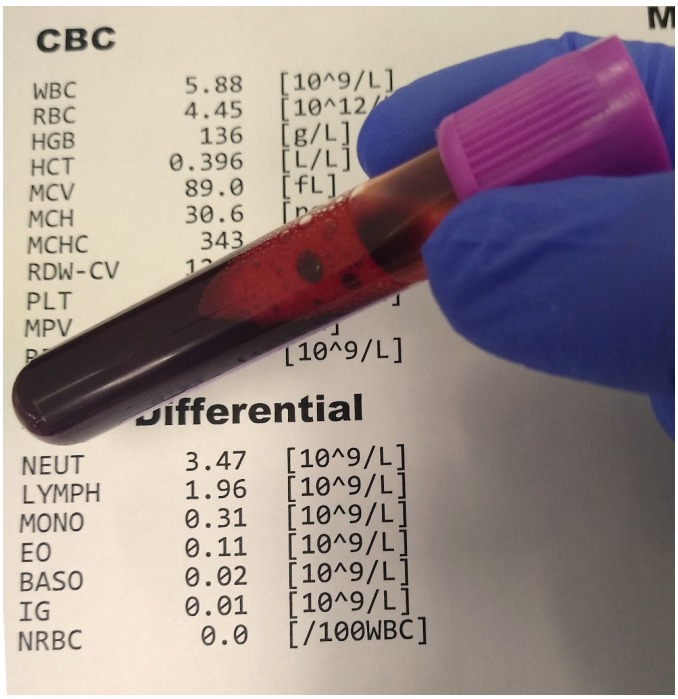
The CBC



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WBC	3.0 x10^9/L	(4.5 - 11.0)
RBC	4.64 x10^12/L	(3.80 - 5.20)
Hgb	126 g/L	(117 - 161)
Hct	0.36 L/L	(0.35 - 0.47)
MCV	76.9 fL	(81.0 - 102.0)
MCH	27.2 pg	(27.0 - 35.0)
MCHC	353 g/L	(310 - 360)
Platelet	255 x10^9/L	(140 - 400)
RDW-CV	16.0 %	(11.5 - 14.8)
MPV	12.00 fL	(9.60 - 12.00)
Retic Cnt Auto %	1.4 %	(0.5 - 2.5)
Retic Cnt Auto #	66.80 x10^9/L	(50.00 - 100.00)
Imm Retic Frac	14 %	
Neutro %	22.30 %	
Lymph %	59.30 %	
Mono %	14.10 %	
Eos %	3.00 %	
Baso %	1.30 %	
Neutro #	0.66 x10^9/L	(2.00 - 9.00)
Lymph #	1.76 x10^9/L	(1.00 - 3.30)
Mono #	0.42 x10^9/L	(0.00 - 1.00)
Eos #	0.09 x10^9/L	(0.00 - 0.70)
Baso #	0.04 x10^9/L	(0.00 - 0.15)

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What is anemia

- Anemia is defined as:
  - Decrease red blood cells (RBCs) and/or
  - Decreased hemoglobin and/or
  - Decreased hematocrit
- This must be compared with the defined normal ranges for age and gender.
- RBC parameters are usually highest at birth and ranges are higher in males after puberty

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Epidemiology

- Incidence: Iron deficiency anemia and hemoglobinopathies (conferring resistance to malaria) are very high (billions of people)
  - Acquired anemia is more common than constitutional anemia
- Age: Constitutional anemia manifests in the neonatal period or infancy
  - Acquired anemia can occur anytime throughout life
  - Iron deficiency anemia is common in women of reproductive age and children
    - Predominates in children and women in poor socioeconomic conditions
- Gender: Constitutional anemia has no gender association, except glucose-6-phosphate dehydrogenase deficiency (X-linked autosomal recessive).

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Constitutional Anemias

- Bone Marrow Failure: cannot produce adequate RBCs
  - Diamond-Blackfan anemia
- Defective hemoglobin production
  - Thalassemia and hemoglobinopathies
- Intrinsic erythrocyte survival defects
  - Hereditary spherocytosis and G6PD deficiency
- Hereditary microangiopathic anemias
  - ADAMTS13 deficiency linked to extrinsic defect reducing RBC survival

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Acquired anemias

- Production
- Maturation
- Survival defects

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Mechanistic classification

1. Production defects
2. Maturation disorders
3. Survival defects

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Production defect:

- Failure of the bone marrow to produce adequate erythrocytes
  - Diverse bone marrow failure disorders
  - Defective erythropoietin production by the kidney
  - Bone marrow effacement by infiltrative or fibrotic processes
  - Aplastic anemia
  - Red cell aplasia
  - Paroxysmal nocturnal hemoglobinuria

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Maturation disorders affecting erythrocytes

- Nuclear:
  - Impaired DNA synthesis and mitosis
  - Deficiencies of vitamin B12 or folate
  - Chemotherapeutic agents
- Cytoplasmic:
  - Defective production of hemoglobin
  - Iron deficiency
  - Globin chain production disorders (thalassemia)
  - Heme biosynthetic disorders (sideroblastic anemia)

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Erythrocyte survival defects

- Intrinsic:
  - Membrane defects (hereditary spherocytosis)
  - Hemoglobin defects (sickle cell)
  - Enzyme deficiencies (G6PD deficiency)
- Turbulent blood flow (mechanical valve)
- Microangiopathies
- Diverse immune mediated hemolytic anemias

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Work-up

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Clinical Approach

- Age and duration of onset
- Severity of symptoms
  - Sudden vs gradual
  - Episodic vs sustained
- Clinical history should address menstrual and GI symptoms (specifically looking for blood loss)
- Dietary history (homeopathic remedies and supplements)
- Exposures
  - Occupation
  - Hobbies
  - Medications

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Clinical Approach

- Family history
- Racial/ ethnic background
- Evaluate underlying chronic disease
  - Liver and kidney disease
  - Collagen vascular disease
  - Endocrine abnormalities
  - Chronic infections

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Physical Exam

- Stigmata of constitutional disorders
- Jaundice
- Spleen size
- Mucosa
- Nails
- Fingers
- Neurologic features

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Laboratory Tests

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Complete Blood Cell Count (CBC) and differential

- Evaluates the size, shape, hemoglobin content and uniformity of RBCs
- Polychromasia and nucleated RBCs
- RBC inclusions, organisms, agglutination, rouleaux
- Assess white blood cell (WBC) lineage and platelets

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Reticulocyte count

- Evaluates whether there is appropriate bone marrow response to anemia
  - Low: Production or maturation disorder
  - Normal: Some cases of anemia of chronic disease
  - Elevated: Hemolytic anemias

Customize further testing based on microcytic, normocytic and macrocytic findings on the CBC

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Microcytic, Normocytic and Macrocytic

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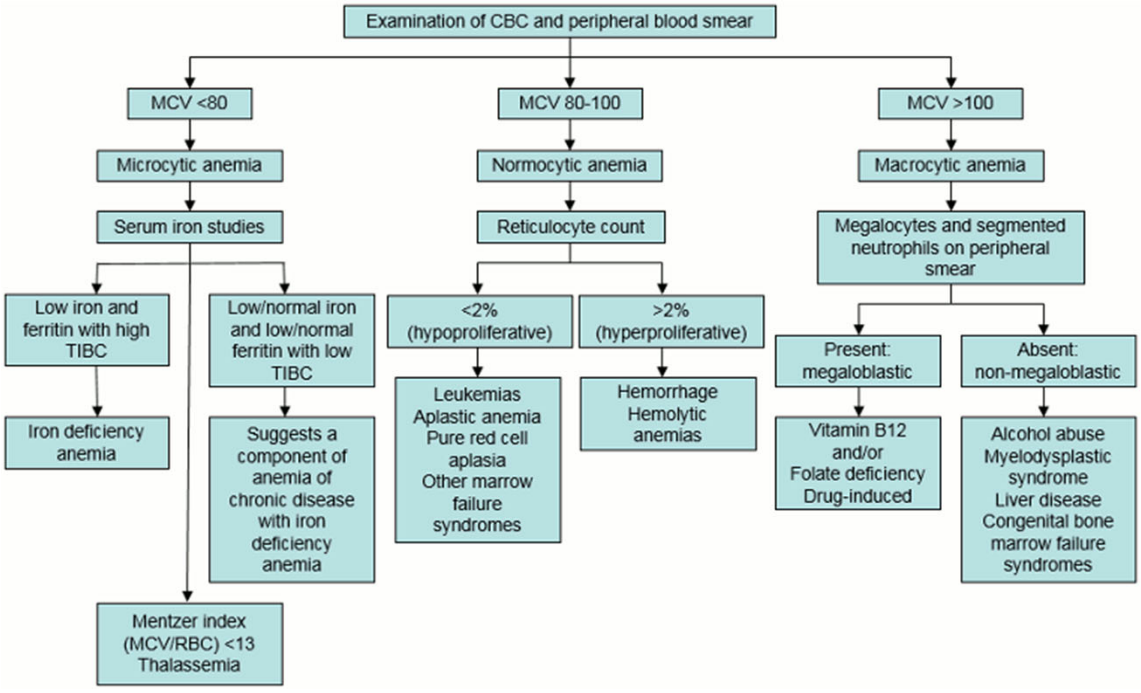

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Microcytic Anemia

- Iron deficiency
- Anemia of chronic disease
- Thalassemia
- Hemoglobin E

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Normocytic

- Suspect anemia of chronic disease
- Bone marrow may be necessary to exclude other considerations

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Macrocytic

- Megaloblastic anemia (rarely, but can be normocytic)
  - Cobalamin and folate levels
- Reticulocytosis (peripheral smear should show polychromasia)
- Hypothyroidism
- Liver disease
- Ethanol use
- Medications
- Myelodysplasia (assess all cell lineages on PBS)

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Anemia of Chronic Disease

Anemia seen with acute or chronic inflammatory conditions, infections, end-stage organ failure or malignancy

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Etiology

- Cytokine/other immune regulatory factors cause multiple iron metabolic disturbances
- Decreased iron absorption in GI tract
- Accumulation of iron in reticuloendothelial system
- Inability to release stored iron to plasma, hypoferremia
- Diminished iron available to erythroid precursors for hemoglobin synthesis
- Blunted bone marrow response to erythropoietin

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Clinical and Laboratory Presentation

- Mild anemia
- Symptoms related to underlying disease usually predominate
- Decreased serum iron
- Normal to increased serum ferritin
- Decreased total iron binding capacity (TIBC)
- Decreased serum transferrin saturation %
- Normal serum transferrin receptor concentration
- Increased plasma/serum and urine hepcidin levels

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Pathology

- Injury type
  - Proliferation defect
- Cell type
  - Erythrocyte
- PBS
  - N/N anemia
  - Mild anisocytosis with normal RDW
  - Low reticulocyte count (decreased polychromasia)
- BM
  - Normal number of erythroid progenitors
  - Increased storage in macrophages and histiocytes
  - Decreased sideroblasts (iron containing erythroid progenitors)

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Differential

- Iron deficiency
- Anemia of chronic renal failure
  - Anemia secondary to decreased erythropoietin levels
  - BM shows erythroid hypoplasia
- Multifactorial Anemia
  - Patients with renal failure, hepatic failure, AIDS, endocrine disorders ect
  - Needs clinical correlation

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Diagnostic checklist

- Most common type of anemia in hospitalized patients
- Usually mild
- N/N
- Develops 1-2 months after illness onset
- Work-up interpretation:
  - Decreased serum iron
  - Decreased TIBC
  - Decreased transferrin saturation
  - Normal to increased serum ferritin
  - Normal soluble serum transferrin receptor levels
  - Increased plasma/serum and urine hepcidin levels

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Iron deficiency anemia

Decreased hemoglobin production secondary to decreased iron availability

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Etiology

- Inadequate hemoglobin production leads to microcytic hypochromic RBCs
- Most common anemia, affects 3 billion people worldwide

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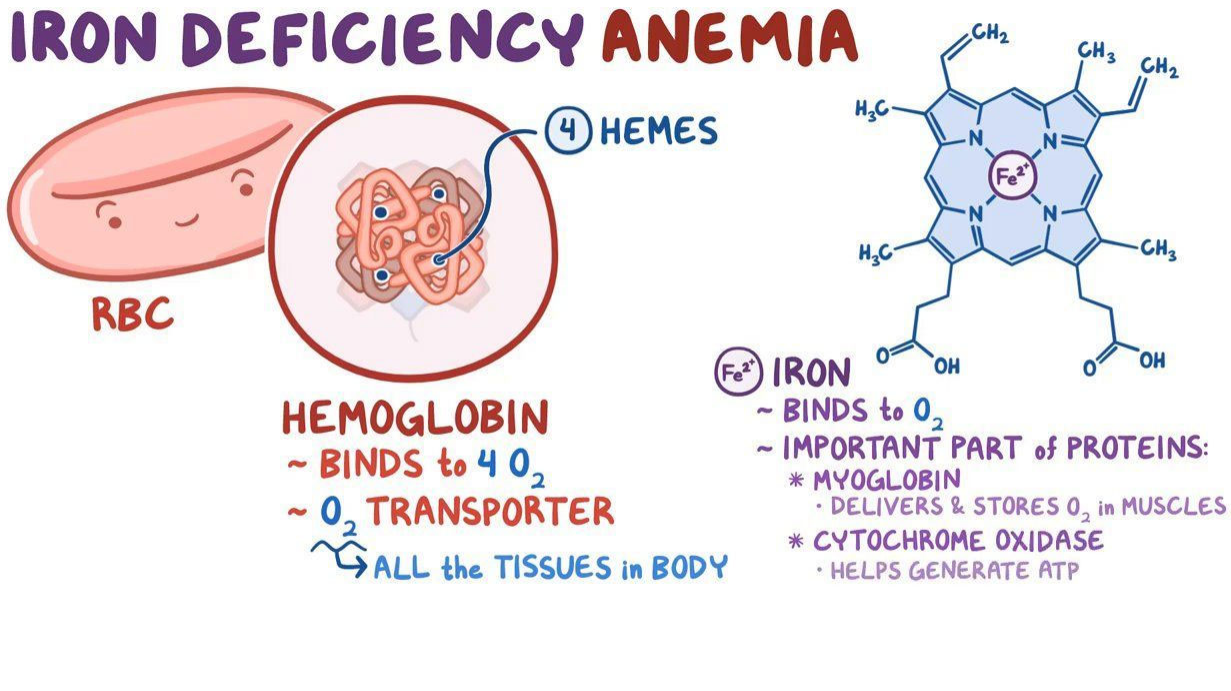

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Clinical Presentation

- Fatigue
- Pallor
- Weakness
- Tachycardia
- Dyspnea on exertion
- Koilonychia (spoon nail)
- Glossitis
- dysphagia

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Laboratory Testing

- Microcytic/hypochromic
- Decreased serum iron
- Decreased serum ferritin
- Increased TIBC
- Decreased serum transferrin saturation %
- Increased serum transferrin receptor concentration
- Decreased serum hepcidin

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Pathology

- Injury type
  - Decreased hemoglobin synthesis
- Cell type
  - Erythrocyte
- PBS
  - Decreased RBC count
  - Mild to marked anemia with severe anisopoikilocytosis (increased RDW)
  - Microcytic (decreased MCV), hypochromic (decreased MCHC)
- BM
  - Erythroid hyperplasia
  - Decreased iron storage and sideroblasts

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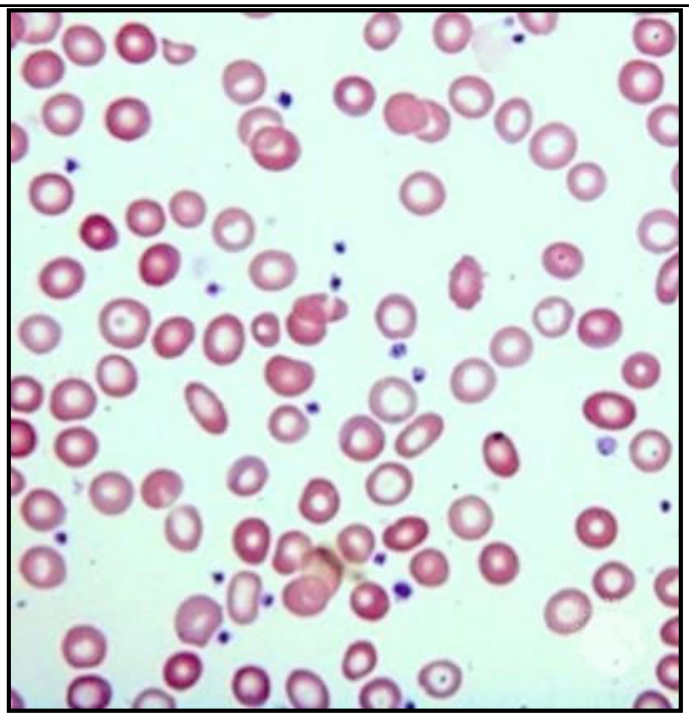

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Differential

- Thalassemia Minor
  - Normal or increased RBC count
  - Normal RDW
  - Numerous target cells
- Anemia of chronic disease
- Lead poisoning
  - Course basophilic stippling
  - Numerous ring sideroblasts in BM
  - Blood lead level high (diagnostic)
- Sideroblastic anemia
  - N/N
  - Increased iron storage
  - Increased BM ring sideroblasts (greater than 10%)

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Diagnostic checklist

- Microcytic/hypochromic
- Decreased serum iron
- Decreased serum ferritin
- Increased TIBC
- Decreased serum transferrin saturation %
- Increased serum transferrin receptor concentration
- Decreased serum hepcidin

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Megaloblastic Anemia

Ineffective hematopoiesis resulting from disorders of DNA synthesis – usually vitamin B12 or folate

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Etiology: Vitamin B12 or folate deficiency

- Inadequate intake (more common with folate)
  - Populations at risk
    - Elderly
    - Indigent
    - Chronic alcoholics
    - Pregnant women and infants
- Absorption defects (more common with B12)
  - Deficiencies, antibodies against and intrinsic factor
  - Medications

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Clinical Presentation

- Anemia, in more severe cases all 3 cell lineages may be decreased (pancytopenia).
- Neurologic impairment
  - More common in vitamin B12
  - Peripheral neuropathy
  - Subacute combined degeneration of the spinal cord
  - Focal demyelinization of white matter of the brain
- Glossitis
- GI distress
- Weight loss
- Problems with fertility
- Hypohomocysteinemia (may lead to stroke)

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Laboratory Testing

- Macrocytic/normochromic (increased MCV normal MCHC)
- Marked anisopoikilocytosis (increased RDW)
- Pancytopenia in severe cases
- Screening tests
  - Serum vitamin B12
  - Serum folate
  - RBC folate

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Additional testing if screening is equivocal

- Methylmalonic acid (MMA)
  - Elevated in vitamin B12 deficiency, not in folate deficiency
  - More specific than serum vitamin B12
- Schillings test (historic)
  - Helpful in diagnosing pernicious anemia
  - Measures absorption of orally administered vitamin B12 +/- intrinsic factor
- Intrinsic factor blocking antibodies
- Parietal cell antibodies

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Pathology

- Injury type
  - Due to ineffective hematopoiesis with intramedullary cell death – rapid cell turnover with frequent mitotic figures
- Cell type
  - Erythroid lineage – all lineages affected, especially granulocytes
- PBS
  - Macrocytic anemia
  - Anisopoikilocytosis (RDW) worsens with severity of deficiency
  - Howell-Jolly bodies, basophilic stippling, or Cabot rings (severe deficiency)
  - Hypersegmented neutrophils (can be earliest sign)
  - Pancytopenia when severe
- BM
  - Hypercellularity of all cell lineages, but erythroid most prominent
  - Megaloblastic changes in multiple lineages
  - No increase in myeloblasts

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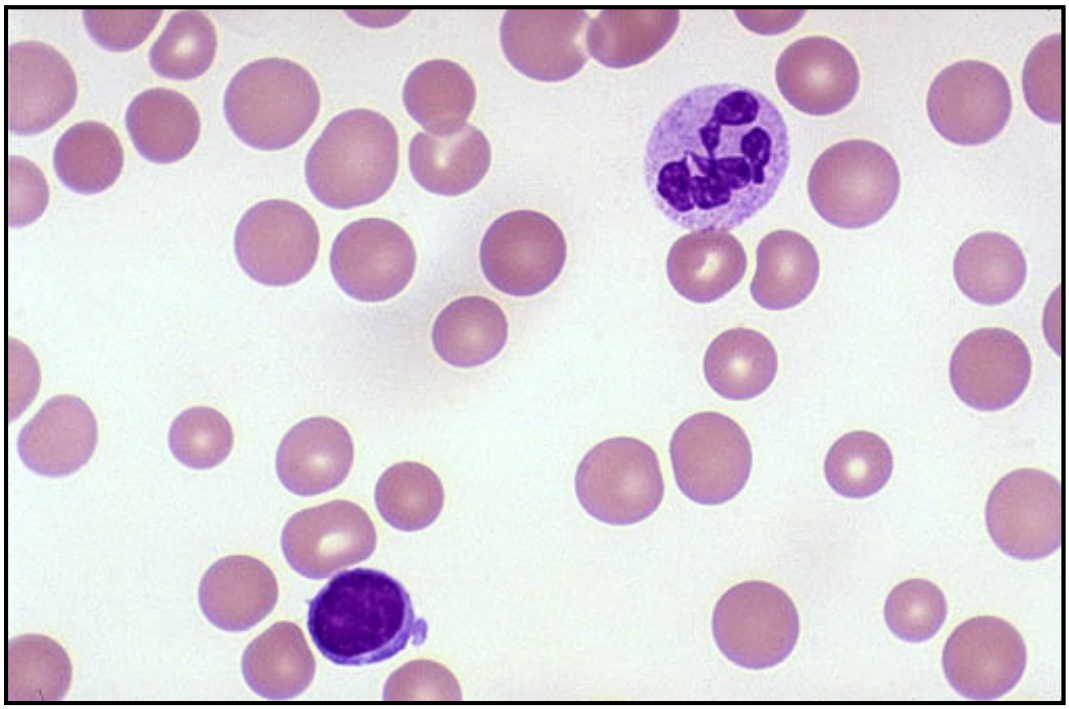

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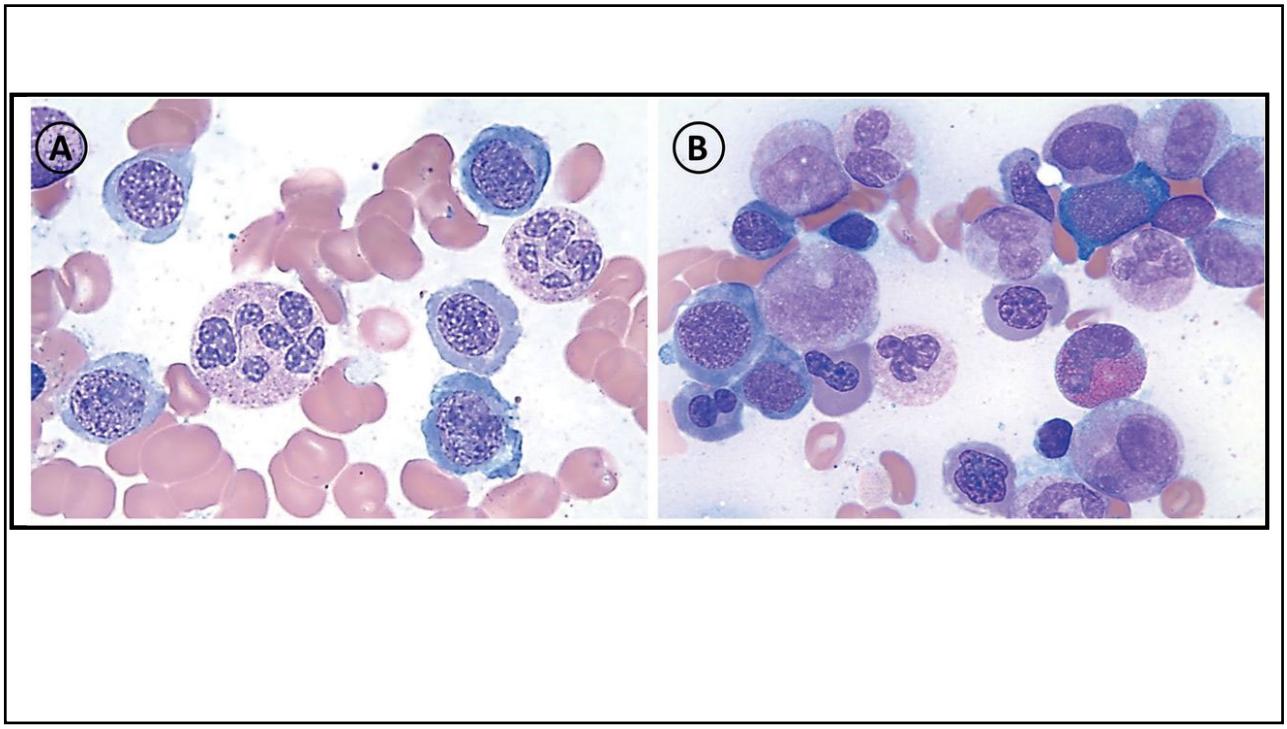

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Differential

- Myelodysplastic syndrome
  - Cytogenetic abnormalities
  - Dysplasia
  - Increased blasts
- Acute erythroid leukemia
- Medications and toxins
- Collagen vascular disease
  - Often see megaloblastoid changes in erythroid nuclei and presents with cytopenias

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Diagnostic checklist

- Macrocytic anemia with elevated RDW
- Hypersegmented neutrophils
- Trilineage hyperplasia in BM
- Megaloblastic changes
  - Erythroid with fine sieve like chromatin
  - Granulocytes with enlarged nuclei, fine chromatin (giant bands)
  - Nuclear - cytoplasmic dissociation (nuclei less mature than cytoplasm)
  - If vitamin deficiency can be demonstrated a bone marrow biopsy is not necessary

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Microangiopathic hemolytic anemia

Fragmentation of red blood cells due to narrowing or obstruction of microvasculature

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Major types of MAHA

- Thrombotic thrombocytopenic purpura (TTP): ADAMTS13 is severly deficient
  - Congenital
  - Aquired
- Hemolytic uremic syndrome (HUS): Damage to endothelial cells; microthrombi formation
- Disseminated intravascular coagulation (DIC): Tissue factor or bacterial toxin activation of coagulation cascade

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TTP

- Congenital : rare present at birth
  - Mutations of ADAMTS13
- Acquired: predominant subtype
  - Autoimmune
  - Malignancy
  - Stem cell transplantation
  - Pregnancy
  - Medications
  - Infections (including HIV)

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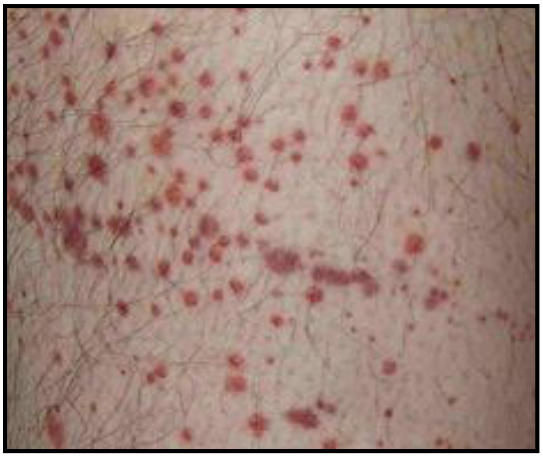
Clinical Presentation

- TTP Triad
  - Thrombocytopenia
  - MAHA
  - Microthrombi of small vessels in multiorgan systems
- Insidious onset
- Fluctuations in neurologic signs in most patients
  - Headaches
  - Bizarre behavior
  - Transient sensorimotor deficits
  - Seizures
  - Coma
- Fever
- Petechiae on lower extremities
- Renal impairment



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Laboratory Testing (common in all types of MAHA)

- Marked thrombocytopenia
- RBC fragmentation and anemia
- Significantly elevated serum lactate dehydrogenase (LDH) level
- Increased indirect bilirubin
- Elevated reticulocyte count

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Laboratory Testing (specific to TTP)

- Normal prothrombin time (PT)
- Normal activated partial thromboplastin time (aPTT)
- Normal DIC panel
  - Fibrinogen
  - D-dimer
- Creatinine level may be elevated
  - ADAMTS13 activity

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Pathology

- PBS
  - Schistocytes (common in all MAHA)
  - Polychromasia, may see nucleated RBCs
  - Thrombocytopenia
  - Leukocytosis
- BM not usually needed

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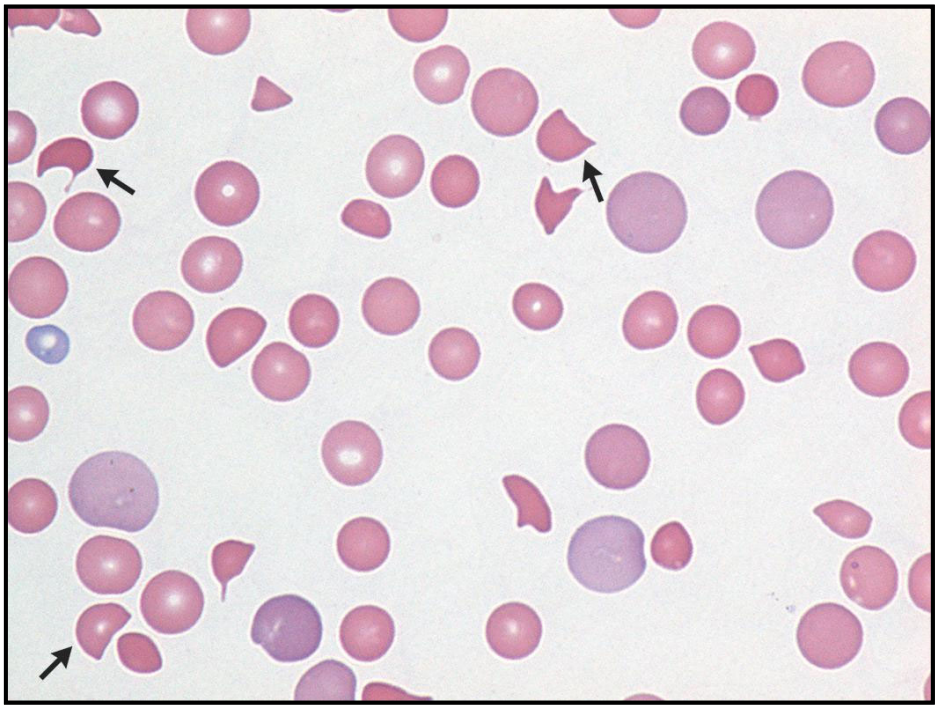

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Diagnostic checklist

- Thrombocytopenia, anemia and schistocytes
- CLINICOPATHOLOGIC CORRELATION REQUIRED

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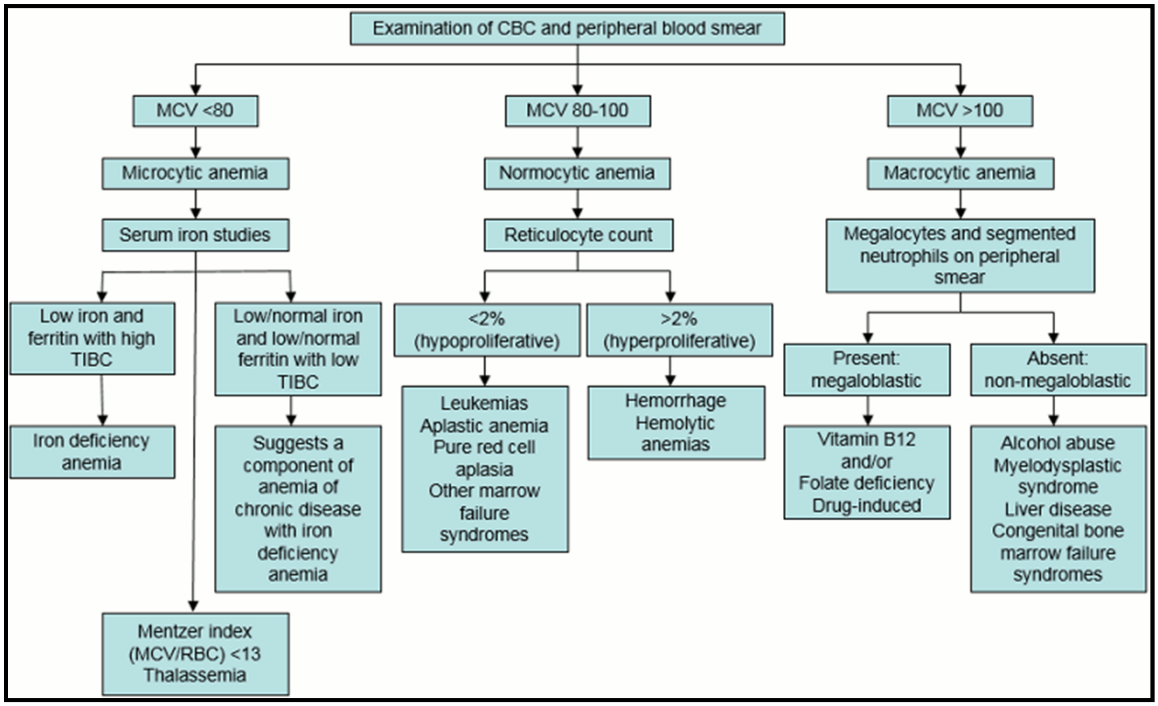

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Please send questions to:

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