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# ANEMIA

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BY  
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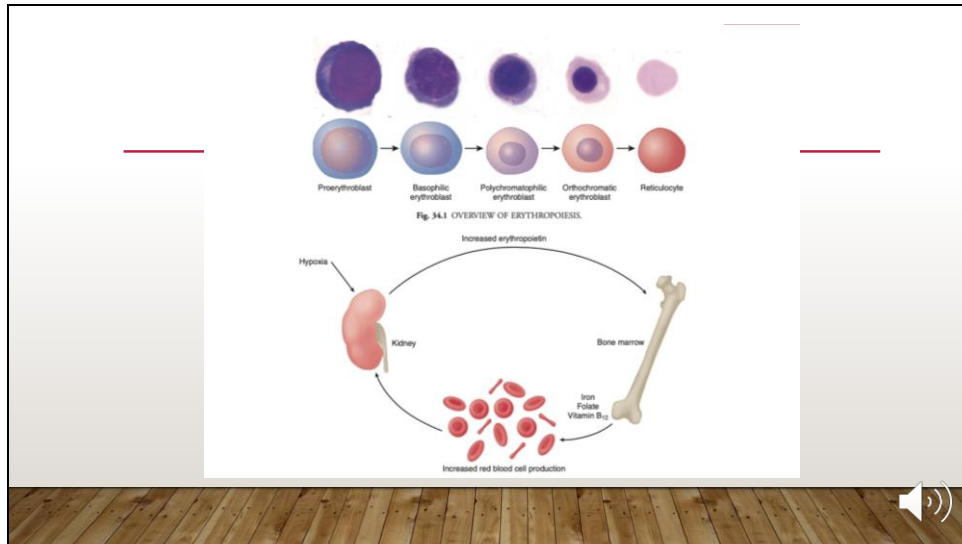
## OBJECTIVES

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-  Define anemia
-  Discuss the different classifications of anemia
-  Discuss the systematic approach to diagnosing anemia
-  Discuss treatment options
-  Review case presentations



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### DEFINE ANEMIA...

- Hemoglobin
- Hematocrit
- RBC count

A microscopic image showing numerous red blood cells (erythrocytes) against a dark background. The cells are biconcave discs, appearing as bright red, circular structures with some central dimpling.

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**Normal hematologic parameters in adults**

Parameter	Males	Females
Hemoglobin (g/dL)	13.6 to 16.9	11.9 to 14.8
Hematocrit (%)	40 to 50	35 to 43
RBC count ( $\times 10^9/\text{microl}$ )	4.2 to 5.7	3.8 to 5.0
MCV (fL)	82.5 to 98	
MCHC	32.5 to 35.2	
RDW (%)	11.4 to 13.5	
Reticulocyte count ( $\times 10^9/\text{microl}$ , or $\times 10^9/\text{L}$ )	16 to 130	16 to 98
Platelet count ( $\times 10^9/\text{microl}$ )	152 to 324	153 to 361
WBC count ( $\times 10^3/\text{microl}$ )	3.8 to 10.4	

These parameters were determined for approximately 1500 to 2000 individuals ages 20 to 80 (varies slightly by category). Reference ranges may differ depending on the instrument used. Refer to the laboratory-specific reference values provided with the individual's results.

CBC: complete blood count; RBC: red blood cell; MCV: mean corpuscular volume; fL: femtoliter; MCHC: mean corpuscular hemoglobin concentration; RDW: red cell distribution width; WBC: white blood cell.

Data from:

1. Adeli K, Razman JE, Chen Y, et al. Complex Biological Profile of Hematologic Markers across Pediatric, Adult, and Geriatric Ages: Establishment of Robust Pediatric and Adult Reference Intervals on the Basis of the Canadian Health Measures Survey. *Clinical Chemistry* 2015; 61:1075.
2. Van den Bosché J, Devesse K, Halford R, et al. Reference Intervals for a Complete Blood Count Determined on Different Automated Hematology Analyzers: Abx Pentia 120 RetC, Coulter Gen-S, Sysmex SE 9500, Abbott Cell-Dyn 4000 and Bayer Advia 120. *Clin Chem Lab Med* 2002; 40:69.

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## RETICULOCYTE PRODUCTION

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Reflects state of erythropoiesis



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## REASONS FOR ABNORMAL RANGES

- Causes of lower values
  - Ethnicity
  - Intense physical activity
  - Pregnancy
  - Older age
- Causes of higher values
  - Smoking
  - Hemoconcentration
  - High altitude





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## **CATEGORIES OF ANEMIA**

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- Blood loss anemia
- Hypoproliferative anemia
- Hemolytic anemia





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## **BLOOD LOSS ANEMIA**

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- acute
- chronic



## HYPOPROLIFERATIVE ANEMIA CAUSES

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- iron deficiency
- anemia of chronic disease
- renal disease
- folate deficiency
- vitamin B12 deficiency
- alcohol
- myelodysplastic syndrome
- myelofibrosis
- acute leukemia




## IRON DEFICIENCY ANEMIA

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- Serum iron
- Total iron binding capacity (TIBC)
- Transferrin saturation
- Ferritin (most reliable indicator of iron stores)

\* Determine source of bleeding




## HEMOLYTIC ANEMIA CAUSES

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Congenital causes:

- Hemoglobinopathies
- G6PD deficiency
- Thalassemia
- Sickle cell disease
- Hereditary spherocytosis




## HEMOLYTIC ANEMIA CAUSES

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Acquired causes

- Autoimmune hemolytic anemia
- Microangiopathic hemolytic anemia - disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP)
- Infections
- Acquired disorders caused by liver disease
- Paroxysmal nocturnal hemoglobinemia




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**MICROCYTIC ANEMIA**  
MCV <80

Hereditary disorders

- Defects of globin synthesis
  - Thalassemia syndromes**
  - Thalassemic hemoglobinopathies
- Defects of iron metabolism
  - Iron refractory iron deficiency anemia
  - Divalent metal transporter 1 mutations
  - Atransferrinemia
  - Sideroblastic anemia




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**MICROCYTIC ANEMIA**  
MCV <80

Acquired disorders

- **Iron deficiency anemia**
- Anemia of chronic disease/anemia of inflammation
- Myelodysplastic syndrome with acquired thalassemia
- Sideroblastic anemia due to drugs or toxins (lead poisoning, alcohol, drugs)
- Copper deficiency
- Zinc toxicity






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**NORMOCYTIC ANEMIA**  
**MCV 80-100**

- Bleeding (acute)
- Hemolysis
- Iron deficiency (early)
- Anemia of chronic disease/inflammation
- Bone marrow suppression (cancer, aplastic anemia, infections)
- Chronic renal insufficiency
- Hypothyroidism
- Hypopituitarism
- Excess alcohol
- Copper deficiency
- Zinc poisoning



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**MACROCYTIC ANEMIA MCV > 100**

**Abnormalities of DNA metabolism**

- Vitamin B12 deficiency
- Folate deficiency
- Drugs (Antiretroviral therapies, Azathioprine, Capecitabine, Cladribine, Cytosine arabinoside, Hydroxyurea, Imatinib, Sunitinib, Methotrexate)

**Shift to immature or stressed red cells**

- Reticulocytosis
- Action on erythropoietin
- Aplastic anemia/Fanconi anemia
- Pure red cell aplasia



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Primary bone marrow disorders

- Myelodysplastic syndromes
- Congenital dyserythropoietic anemias
- Some sideroblastic anemias
- Large granular lymphocyte leukemia


Lipid abnormalities

- Liver disease
- Hypothyroidism

Mechanism unknown

- Alcohol abuse
- Multiple myeloma and other plasma cell disorders


## MACROCYTIC MCV >100



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### MEAN CORPUSCULAR VOLUME (MCV) AND RED BLOOD CELL DISTRIBUTION WIDTH (RDW)

MCV, RDW	Reticulocyte count <100,000/	Reticulocyte Count greater than or equal to 100,000/
Low, Normal	Anemia of Chronic Disease	
Normal, Normal	Anemia of Chronic Disease	
High, Normal	Chemotherapy, antivirals, alcohol, Aplastic anemia	Chronic Liver Disease
Low, High	Iron deficiency anemia	Sickle Cell B-thalaseemia
Normal, High	Early iron, folate, vitamin b12 deficiency, myelodysplasia	Sickle Cell anemia, sickle cell disease
High, High	Folate or vitamin b12 deficiency, myelodysplasia	Immune Hemolytic anemia, chronic liver disease




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## SYSTEMATIC APPROACH TO ANEMIA

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- History and Physical Examination
- Review Complete Blood Count (CBC) including the Mean Corpuscular Volume (MCV) and Red Blood Cell Distribution Width (RDW)
- Review the Reticulocyte Count
- Review the Peripheral Blood Smear
- Bone Marrow Biopsy




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## SYSTEMATIC APPROACH TO ANEMIA

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- Medical History
- Review Medications
- Occupational History
- Social History
- Dietary History
- Family History
- Physical examination



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**DRUGS ASSOCIATED WITH ANEMIA**

- Iron deficiency anemia- aspirin, NSAIDs, glucocorticoids
- Vitamin B12 deficiency-proton pump inhibitors, H2 receptor blockers, antacids, metformin and nitrous oxide
- Folate deficiency-methotrexate, certain antibiotics (trimethoprim, pyrimethamine) and antiseizure medications (phenytoin, valproate, carbamazepine)
- Hemolysis-antibiotics, anti-cancer drugs, lorazepam, phenazopyridine, benzocaine, lidocaine, nitrates, quinine, chemotherapy agents, immunosuppressive therapies, hydroxyurea, isoniazid, chloramphenicol, linezolid, zinc and alkylating agents





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**SIGNS AND SYMPTOMS OF ANEMIA**

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- Fatigue
- Symptoms that suggest hemolysis  
(dark urine, jaundice, history of gallstones, anemia with certain food or drug exposure).
- Symptoms of kidney, disease, liver disease and hypersplenism



## PHYSICAL EXAMINATION


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- Pallor on examination
- Angular cheilitis
- Koilonychia
- Heart murmur
- Splenomegaly
- Neurological-loss of vibration



## DIAGNOSTICS AND TREATMENT


- Type and crossmatch/blood transfusion
- Provide hemodynamic support
- Complete blood count including MCV and RDW
- Reticulocyte count
- Peripheral blood smear
- Liver biochemical tests (total and indirect bilirubin, alanine aminotransferase ALT and aspartate aminotransferase AST)
- Kidney function (creatinine and blood urea nitrogen)
- Assess for new onset hemolysis (LDH, Haptoglobin)



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**DIAGNOSTICS  
AND  
TREATMENT**

- Cytopenias, abnormalities of cell lines
- Bone marrow biopsy
- C-reactive protein, ESR
- Iron studies, vitamin B12, folate level, thyroid studies
- Direct antiglobulin (Coombs) test
- Copper level
- Prothrombin time (PT) and activated partial thromboplastin time (aPTT)



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**Peripheral Blood Smear**

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Confirm automated CBC count

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Reveals changes seen in hemolytic disorders

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**Bone Marrow Biopsy**

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Flow cytometry and fluorescence in situ hybridization (FISH) and molecular testing



42 year old male in seen to establish care. Other than history of chronic anemia with poor response to oral iron therapy he has no other significant medical history.

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HGB 10.2 g/dL, RBC 6.2 million/uL, MCV 70 fL, RDW 12%, reticulocyte 80,000/uL (1.3%), WBC 5,500/uL, PLT 230,000/uL

CASE I



## CASE I

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- What is the most likely diagnosis?
  - Iron deficiency
  - Anemia of chronic disease (inflammation)
  - Thalassemia



CASE 2

37 year old homeless woman with history of heavy alcohol use is evaluated for anemia. Laboratory results show HGB 6.8 g/dL, MCV 127 fL, RDW 15.7%, WBC 4,200/uL, PLT 152,000/uL, folic acid 1 ng/mL, vitamin B12 425 pg/mL, transferrin saturation 20%.

Therapy with folic acid is started.





CASE 2

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Differential diagnosis:

- macrocytosis
- folic acid deficiency
- drugs
- Alcohol
- Reticulocytosis
- Liver disease
- Hypothyroidism
- Myelodysplastic syndrome





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**CASE 3**


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57 year old female with a history of vertebral osteomyelitis diagnosed 6 weeks previously is evaluated for anemia.

HGB 8.6 g/dL, MCV 78 fL, RDW 16%, WBC 11,200/uL, Plt 420,000/uL.

Serum iron and TIBC are decreased,

Transferrin saturation 11%, ferritin level 390 ng/mL, CRP is markedly elevated.




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**CASE 3**

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What is the most likely etiology of patient's anemia?

- osteomyelitis
- iron deficiency



## CASE 4

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61 year old male with history of gastric bypass 14 years previously is evaluated for anemia. He reports several recent falls and worsening numbness in distal extremities. His medications include monthly parenteral vitamin B12 and oral multivitamins.

HGB 8.1 g/dL, MCV 101 fL, WBC 2,100/uL, PLT 190,000/uL. LDH is normal, liver chemistries are within normal range.



## CASE 4

What is the most likely explanation of patient's condition?



## CASE 5

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23 year old male is evaluated for anemia. He reports a 1 week history of sore throat and fever. Enlarged cervical lymph nodes are palpated.

Laboratory evaluation shows HGB 10.7 g/dL, RBC 2.1 million/uL,  
MCV 149 fL, WBC 15,400/uL, PLT 350,000/uL, reticulocyte 154,000/uL, LDH 375 U/L,  
indirect bilirubin 2.8 mg/dL



## CASE 5

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What is the most likely etiology of patient's anemia?

- Folic acid deficiency
- Vitamin B12 deficiency
- Myelodysplastic syndrome
- Hemolysis
- Red cell aplasia



## CASE 5

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Diagnosis: cold agglutinin disease due to acute EBV infection



## CASE 6

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70 year old male with history of COPD, renal impairment and mechanical aortic valve prosthesis placed 6 weeks previously is seen for anemia. Examination discloses both a systolic and diastolic murmur in the aortic area.

HGB 9.1 g/dL, MCV 107 fL, reticulocyte 228,000/uL, PLT 171,000/uL, stable creatinine 2.1 mg/dL, LDH 412 IU/L, indirect bilirubin 2.4 mg/dL. Peripheral slide shows increased schistocytes.



## CASE 6

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What is the most likely explanation for patient's anemia?

Vitamin B12 or folic acid deficiency

Thrombotic microangiopathy

Microangiopathic hemolysis (fragmentation hemolysis)

Liver disease

Anemia of chronic disease



## CASE 7

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45 year old female with history of chronic compensated autoimmune hemolytic anemia is admitted with an acute exacerbation of anemia.

Stool and urine testing for bleeding was negative. Laboratory evaluation shows anemia with HGB 6.1 g/dL, hematocrit 19%, RBC count 1.9 million/uL, reticulocyte 4%, MCV 100 fL, LDH 925 IU/L, indirect bilirubin 3 mg/dL, haptoglobin is undetectable.



## CASE 7

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What is the next most appropriate step in management?

- Initiate prednisone
- Check folic acid and iron levels
- Evaluate for gastrointestinal bleeding



## CASE 8

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62 year old Caucasian female with poorly controlled diabetes mellitus and congestive heart failure is seen to establish care. She reports consuming 4 alcoholic drinks daily. She thinks that a few family members had liver problems. Exam shows obesity with BMI of 42 kg/M2. Laboratory evaluation is significant for ALT 96 IU/L, AST 68 IU/L, ferritin 460 ng/mL, transferrin saturation 55%.



CASE 8

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- What is the most appropriate management?
  - Genetic counseling
  - Genetic screening for hereditary hemochromatosis
  - Address uncontrolled medical problems and secondary conditions of iron overload



CASE 8

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- Elevated transferrin saturation (45%) is consistent with iron overload, while normal value suggests lack of iron overload
- Elevated ferritin level is a sensitive but not specific indicator for iron overload, normal levels suggests lack of iron overload.




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## CASE 8

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Causes of iron overload

- Excessive RBC transfusions
- Ineffective erythropoiesis
- Liver disease
- Alcoholic and non alcoholic liver diseases
- Hereditary hemochromatosis



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## CASE 8

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Causes of elevated ferritin

- Iron overload
- Liver disease
- Infection
- Inflammation
- Diabetes mellitus
- Metabolic syndrome

