# Anemia

Association of Oklahoma Nurse Practitioners
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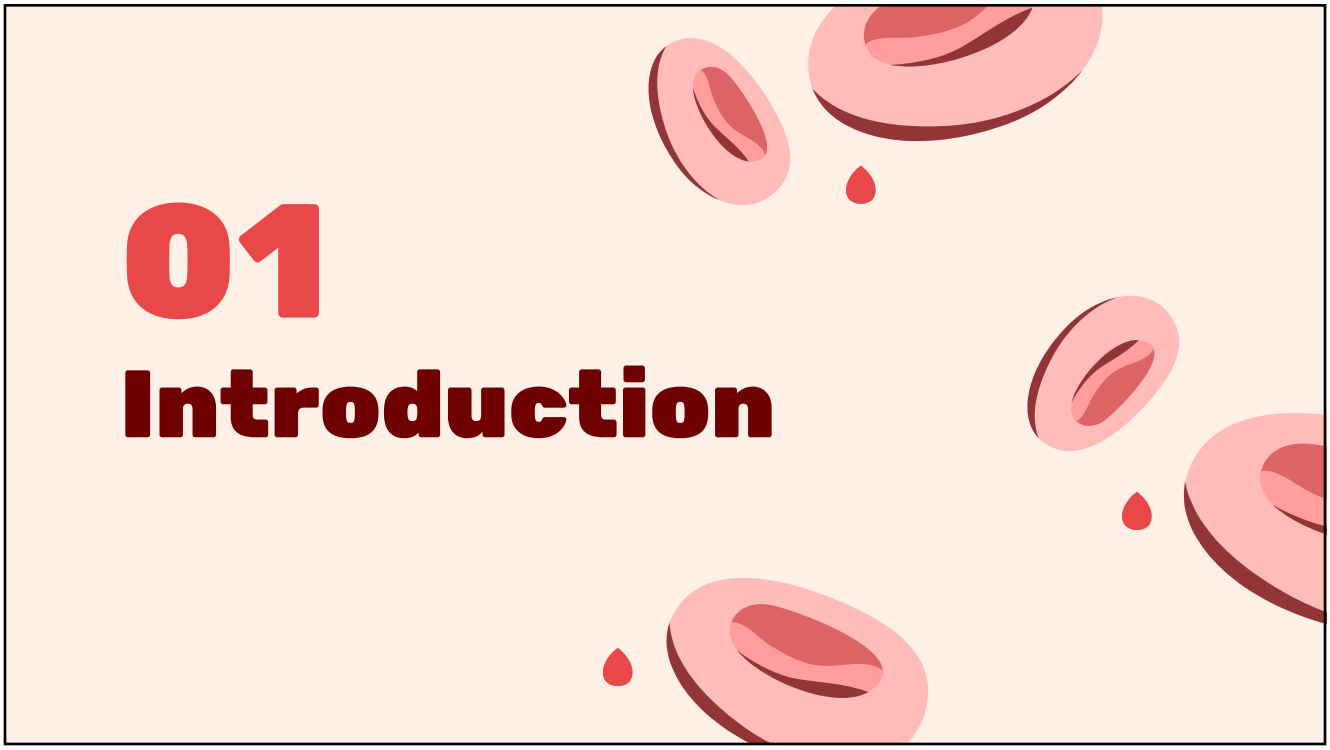


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**Anemia:** Reduction in RBC measurement as part of CBC

- HB, HCT, RBC
- WHO criteria
  - Men Hb < 13
  - Female Hb < 12
- African American have 0.5-1 g/dl lower due to health disparity, high % of alpha thalassemia

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**Caveats for Normal Range:**

Lower Value

- Intense physical activity
- Pregnancy ↑ RBC, ↑ plasma volume, cause relative ↓ Hb, Hct
- Older age

Higher Value

- Smoking
- Hemoconcentration
- High altitude

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## Laboratory Evaluation:

- CBC
- Retic Count
- Chemistry: liver and renal function
- Hemolysis: ↑LDH, ↑ indirect bili, ↑ retic count, ↓ haptoglobin
- RBC morphology
  - Spherocyte immune hemolysis
  - Schistocyte microangiopathic
  - Sickle cell
  - Target Cell, teardrop in thalassemia
- Peripheral smear

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## Approach to Dx:

- H&P
- Underlying medical condition
- Medication
  - NSAIDS, ASA, Glucocorticoid → iron def.
  - PPI, H2 blocker → B12 ↑ pH ↓ absorption
  - Metformin → B12 alter Ca. homeostasis
  - MTX, Bactrim, Anti Seizure → folate def.
  - Dapsone, CMT, immune suppression → hemolysis
  - CMT impair bone marrow function

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## Approach to Dx (continued):

- Family History
- Acquired anemia
  - Diet, vegetarian → B12
  - Travel → parasitic infection
  - Infection
  - Bleeding → heavy menses, melena
- Chronicity of anemia
- Signs of hemolysis  jaundice, dark urine, gallstone
- Symptoms of liver and kidney disease

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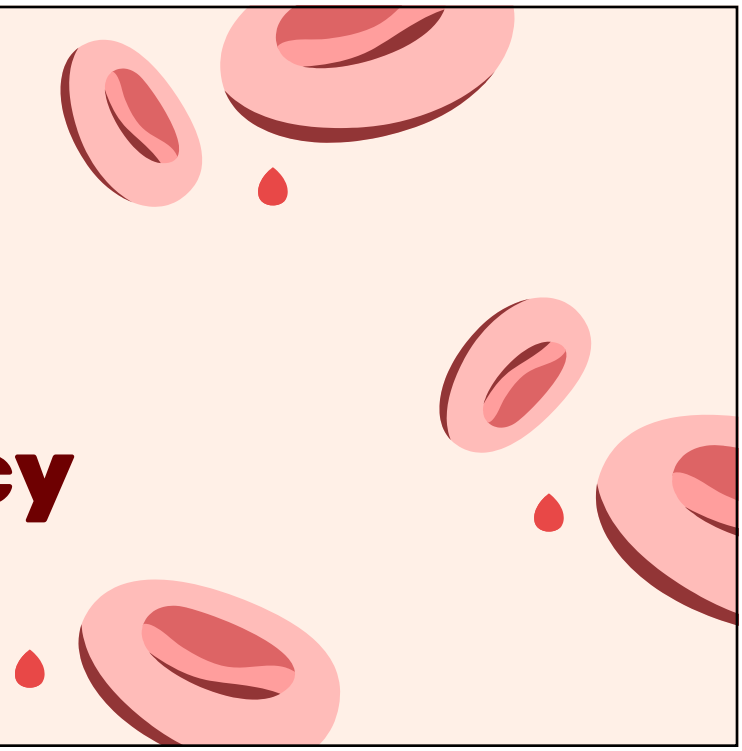
# 03 Iron Deficiency



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# Iron Deficiency Anemia:

- Most common
- 10% of female childbearing age
- Young children
- Elderly - inadequate utilization of iron

- Ferritin < 30 ng/mL
- Transferrin saturation < 19%
- Resolve with iron supplement
- Absence of stainable iron in the bone marrow

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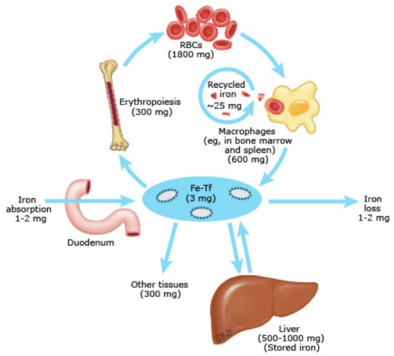
# Iron Absorption and Homeostasis:




Schematic showing iron homeostasis. Fe circulates bound to transferrin, which receives most Fe from macrophages that phagocytize senescent RBCs and by enterocytes that absorb a minimal amount of dietary iron, to compensate for the amount of iron lost through cell desquamation and blood loss. Most Fe is supplied to the bone marrow for RBC production. Excess Fe is stored in the liver and macrophages as a reserve. Numbers (in mg) are an estimate of the mean amount of Fe in various compartments. Refer to UpToDate for details.

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# Etiologies of Iron Deficiency:

- Inadequate absorption
  - Poor bioavailability
    - Heme Fe
    - Cow's milk
  - Inhibitor of absorption
  - Bran, starch, metals
  - Absorptive surface
- Loss or dysfunction
- Duodenectomy
- Gluten sensitive enteropathy

- Excessive blood loss
  - GI, GU, Pulmonary
- Functional Inaccessibility
  - Anemia of Chronic Disease
  - Inborn/acquired metabolic defects

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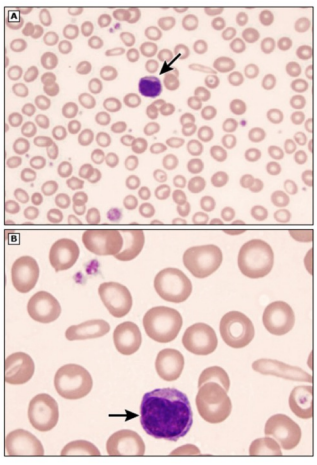
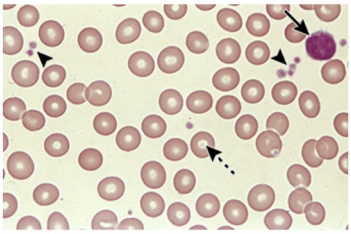
# Peripheral Blood Smear:

**Peripheral blood smear in iron deficiency anemia showing microcytic, hypochromic red blood cells**




The same peripheral blood smear from a patient with iron deficiency is shown at two different magnifications. Small (microcytic) red blood cells are shown, many of which have a thin rim of pink hemoglobin (hypochromia). Occasional "pencil"-shaped cells are also present. A small lymphocyte is shown for size comparison (arrow). Normal red blood cells are similar in size to the nucleus of a small lymphocyte (arrow), and central pallor in normal red blood cells should equal approximately one-third of the cell diameter.

**Normal peripheral blood smear**



High-power view of a normal peripheral blood smear. Several platelets (arrowheads) and a normal lymphocyte (arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (dashed arrow) should equal one-third of its diameter.

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## Iron Deficiency:

Absolute deficiency: lack of endogenous iron

- Causes:
  - Loss of iron (bleeding, phlebotomy, HD, mechanical heart valve, factitious)
  - Decrease intake (diet, no meat, malabsorption, gastric surgery, PPI, IBD, Achlorhydria, Helicobacter)
  - Increased Utilization (pregnancy, rapid growth)
- Lab
  - Ferritin < 20 ng/dL
  - ↓: iron, saturation, RBC count, MCV
  - ↑: transferrin concentration, RDW

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## Iron Deficiency:

Functional deficiency:

- Hypoferremia despite adequate or ↑ iron store
- Causes:
  - Ch. inflammation
  - Ch. infection
  - Neoplasm
  - Recovering from iron deficiency
  - Hemodialysis
- The anemia is mild and asymptomatic
  - NC, MCV Low end of normal
  - ↓ iron and saturation
  - ↑ ferritin

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# Treatment of Absolute Iron Deficiency:

- Oral iron
- Iron Salts
  - Ferrous sulfate, gluconate
  - Iron Polysaccharide
  - Niferex and ferrex
  - Take with food ↓ N, ↓ absorption
  - Ascorbic acid doesn't enhance absorption
  - Slow iron → less GI symptoms, less iron, may release below duodenum, less absorption
  - Medication ↓ absorption
    - Antacid, cycline, pancreatic enzyme, bisphosphonate,
    - Calcium, tea, dairy, vegetables ↓ absorption
    - Lean meat intake - haem readily absorbed

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# Lack of Response to Oral Iron:

| |
|---|
| **A coexisting condition is interfering with bone marrow response to iron repletion** |
| Infection |
| Inflammatory disorder (eg, rheumatoid arthritis) |
| Concomitant malignancy |
| Coexisting folate and/or vitamin B12 deficiency |
| Bone marrow suppression from another cause |
| **Patient is not iron deficient; possible correct diagnoses include** |
| Thalassemia |
| Lead poisoning |
| Anemia of chronic disease/anemia of inflammation |
| Copper deficiency (zinc toxicity) |
| Myelodysplastic syndrome/refractory sideroblastic anemia |
| **Patient is not taking the medication** |
| Prescription has not been filled |
| Prescription has been filled but patient is no longer taking the medication |
| **Medication is being taken but is not being absorbed** |
| Rapid intestinal transport bypasses area of maximum absorption |
| Enteric coated product: coating is not dissolving |
| Patient has an acquired condition that causes malabsorption of iron (eg, sprue, atrophic or autoimmune gastritis, *Helicobacter pylori* infection) |
| Patient is taking an agent that interferes with absorption (eg, antacids, tetracycline, tea) |
| Patient has a congenital cause for iron malabsorption (eg, iron-resistant iron deficiency anemia [IRIDA]) |
| **Continued blood loss or need in excess of iron dose ingested** |
| Treatable cause of blood loss (eg, bleeding peptic ulcer) |
| Cause of blood loss that is not treatable (eg, hereditary hemorrhagic telangiectasia [Osler-Weber-Rendu syndrome]) or need cannot be met by oral iron preparation (eg, kidney failure or a malignancy being treated with erythropoietin) |

The diagnosis of iron deficiency anemia is generally made when there is hypochromic microcytic red blood cells, low ferritin, and low transferrin saturation (TSAT). Refer to UpToDate for approaches to addressing a lack of response to oral iron that depends on the underlying condition, as well as a discussion of indications for switching to intravenous (IV) iron.

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# Treatment (continued):

- IV Iron
  - Indication
  - Side effects, malabsorption, systemic disease
  - Iron dextran (need test dose, 2-3% reaction)
  - Infed ferric gluconate
  - Venofer iron sucrose
- Transfusion
  - Indicated only  for impending complication

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# Oral versus IV Iron:

| | Advantages | Disadvantages |
|---|---|---|
| **Oral iron** | ▪ Effective for most patients<br>▪ Extremely low risk of serious adverse events<br>▪ Initial costs very low | ▪ Gastrointestinal side effects are common<br>▪ Compliance may be low<br>▪ May be inadequate for severe or ongoing blood loss<br>▪ May require administration for several months<br>▪ Total costs may be higher |
| **IV iron** | ▪ Effective for most patients<br>▪ More rapid correction of anemia and resolution of symptoms<br>▪ Ability to administer large doses (up to 1000 mg elemental iron) in a single infusion<br>▪ Compliance is assured<br>▪ No gastrointestinal side effects | ▪ Requires monitored intravenous infusion<br>▪ Rare cases of allergic or infusion reactions<br>▪ Requires equipment and personnel to treat allergic or infusion reactions<br>▪ Initial costs may be higher |

Refer to UpToDate content on the management of iron deficiency for further details. Advantages, disadvantages, costs, and burdens for any individual patient may depend on a number of factors.

IV: intravenous.

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## Treatment (continued):

- Response to treatment
  - ↑ retic count in 3-4 days
  - ↑ Hb 1st week
  - If no response in 1-2 weeks
    - Inaccurate diagnosis, bleeding, malabsorption, or noncompliance, insufficient therapy < 3-6 m

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## Treatment of Functional Iron Deficiency:

- Treat the cause
- Mild anemia
- Iron supplement
- Transfusion to relieve symptoms
- Aim Hb 10-12 > increase risk of CV, thrombosis, mortality, tumor progression
- Respond more to parenteral iron
- EPO indication CRF, HIV, CMT
- Advance malignancy target hemoglobin 10-12 > progression
- Chronic inflammation
  - RA, IBD: respond to parenteral iron, EPO enhance

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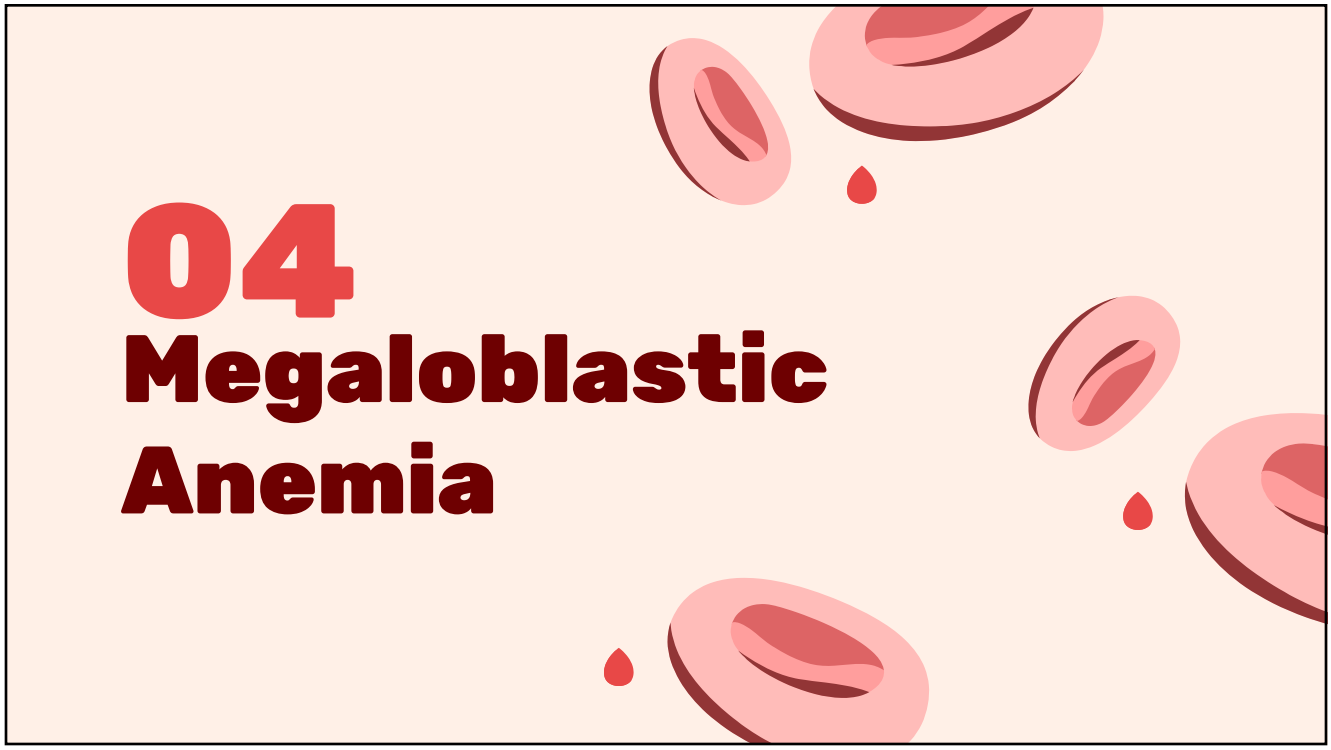
# 04 Megaloblastic Anemia



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## B12 & Folate Deficiency:

- Most common nutritional deficiency anemia
- B12 daily requirement 6 mcg/day, body store 5-10 years
- Folate daily requirement 200 mcg/day, 2-3 months store
- B12 in meat
- Folate in plant, fruit, vegetables

- B12 def. causes megaloblastic changes by restricting folate supply can be overcome by high dose folate

- Hematopoietic effect of folate def. cannot be overcome with B12 therapy
- Cobalamine, neuropsychiatric S & S in B12 def.
- Population at risk European descent > 70, elderly

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## Causes of B12 Deficiency:

- GI
  - Gastric Atrophy
  - Gastric Surgery
  - Terminal ileum resection
  - Severe celiac disease
  - Crohn's of stomach
  - SB bacterial overgrowth
  - ZES, acidify SB, need alkaline for absorption
  - Pancreatic insufficiency
  - HIV
- Medication large dose vitamin C, Metformin, PPI
- Increased utilization, pregnancy
- Diet: strict vegetarian

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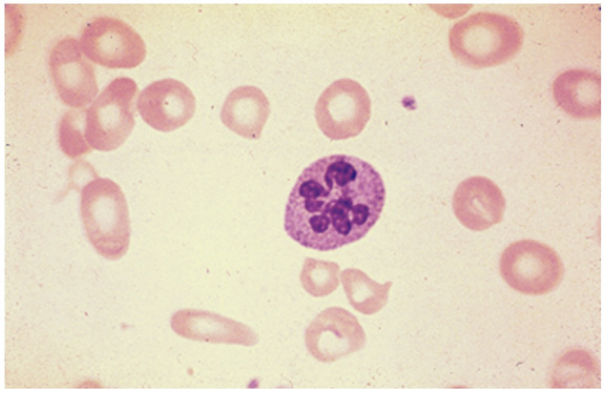
## Megaloblastic Smear:



Peripheral blood smear showing a hypersegmented neutrophil (seven lobes) and macroovalocytes, a pattern that can be seen with vitamin B12 (cobalamin) or folate deficiency.

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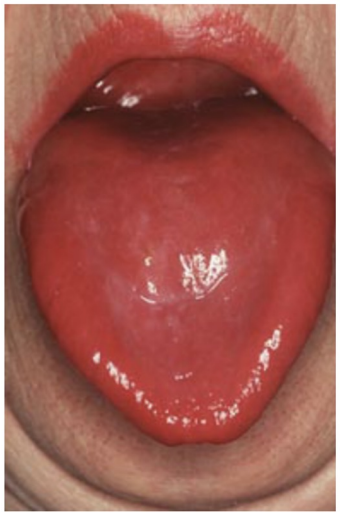
- **Atrophic Glossitis 2:**



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## Causes of Folate Deficiency:

- Diet poor in fresh vegetables
- Disease affecting jejunum
- Pregnancy
- Ethanol
- Medication

## Combine B12 and Folate Deficiency:

- Tropical Sprue
- Gluten sensitive enteropathy

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## Clinical Presentation:

- Peripheral Neuropathy
- Spinal cord degeneration
- Memory loss, disorientation, depression
- Malabsorption -> wt. Loss, diarrhea, glossitis
- Infertility, fetal loss

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## Laboratory:

- Anemia - macrocytic - NC
- Pancytopenia
- Increased LDH when Hb around 10
- Hypersegmented neutrophil
- B12  200 pg/ml, 300 pg/ml
- B12 def. -> increase MMA, homocysteine
- Folate def. Increase homocysteine

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## Non megaloblastic macrocytic anemia MCV 100-110:

- Hemolytic anemia
- Post hemorrhagic anemia
- Alcoholism
- Liver disease
- MDS
- Aplastic anemia
- Hypothyroidism
- Other congenital defect

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## Treatment:

- B12 oral 1-2 mg -> 10-20 mcg absorption
- IM 50-100 mcg daily X one week
  - Weekly X 4 weeks
  - Monthly 1000 mcg

- Folic Acid 1 mg daily for one month
  For SB dysfunction - higher dose and longer duration

## Response:

- Mental change and tongue soreness, immediate
- In 4-5 days increased Retic count, MCV, Hb
- Neuropathy improves slowly, may never resolve

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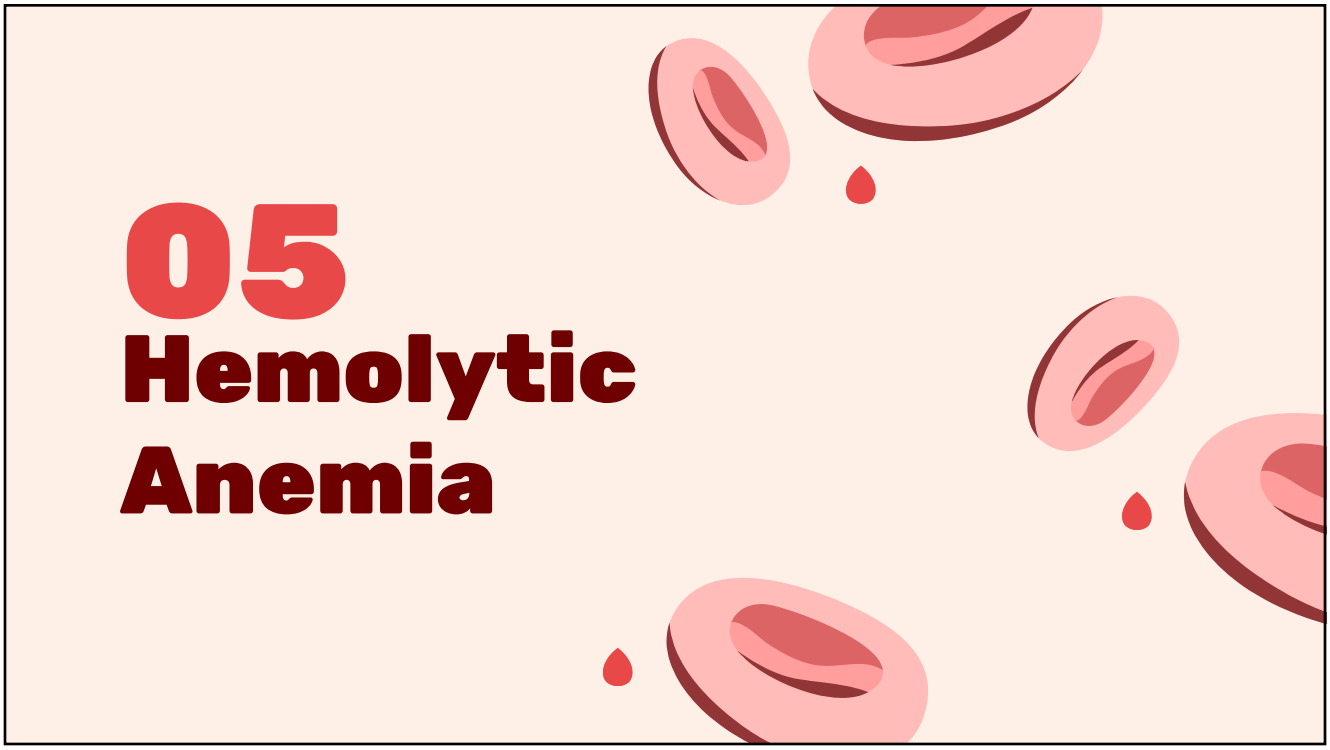


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## Hemolytic Anemia:

- Most common  hemoglobinopathies
  - Immune mediated
- Extra Vascular - due to increased clearance of erythrocyte by RES
- Intravascular - cell lyse within the circulation
- Hallmark - increased retic count
- Patient with underlying defect presents with profound anemia without increased retic count

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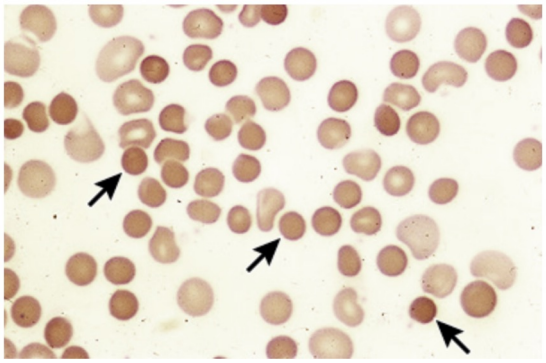
- **Spherocytes:**



Peripheral blood smear shows multiple spherocytes, which are small, dark, dense hyperchromic red cells without central pallor (arrows). These findings are compatible with hereditary spherocytosis or autoimmune hemolytic anemia.

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## Causes of Intrinsic Hemolysis:

- Hb - Hbss, thalassemia, others
- Membrane - hereditary spherocytosis, HUS, PNH
- Enzymes - G6PD, Aldolase, 2, 3 DPG
- Abnormal - Glycoprotein C

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## Causes of Extrinsic Hemolysis:

- Immune - transfusion induced alloantibodies, autoimmune syndrome
- Fragmentation - heart valve, DIC, TTP, HUS, dialysis, malignancy, burn, AVM, vasculitis, runners
- Infection - malaria, clostridium perfringens
- Chemical - oxidant in G6PD, insect or snake venom
- Liver disease, hypersplenism

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## Clinical Approach:

- History and Physical
  - Onset, duration (hereditary or acquired)
  - Jaundice
  - Gallstone in chronic hemolysis
  - Medication - enzyme deficiency
  - Travel: infection
  - Vascular: cardiac surgery
  - Discolored urine:intravascular hemolysis
  - Family history

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## Clinical Approach:

- CBC, peripheral smear
- Increased retic count, MCV, RDW
- ↓ Hemoblogin, ↑ LDH, indirect bilirubin
- Direct Coombs test
- PNH - flow cytometry  CD59
- Hemoglobin electrophoresis
- Culture
- Schistocyte
- Urine hemosiderin
- Splenomegaly
- Absolute retic count -> 100K
- Acute intravascular hemolysis - recognize -> RF, death

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## Enzyme Disorders:

- G6PD Deficiency
  - Most common RBC enzyme disorder
  - X-linked
  - More common in male
  - Common in Mediterranean, African, Chinese

**Class I** Severe - at birth, Chronic hemolysis
**Class II** Severe - intermittent (Medit. and Asian)
**Class III** Moderate - intermittent (assoc. with infec., drug)
**Class IV** No deficiency - no hemolysis
**Class V** Increased enzyme deficiency

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## G6PD Deficiency :

- Qualitative or quantitative deficiency determines degree of hemolysis
- Intracellular oxidative stress - Heinz bodies inclusions during acute and drug induced hemolysis
- Drugs to avoid - Dapsone, Sulfa, Nitrofurantoin, Quinolone and Primaquine

## Treatment:

- Remove the offending agent, drug
- Blood transfusion
- Splenectomy if no response to therapy

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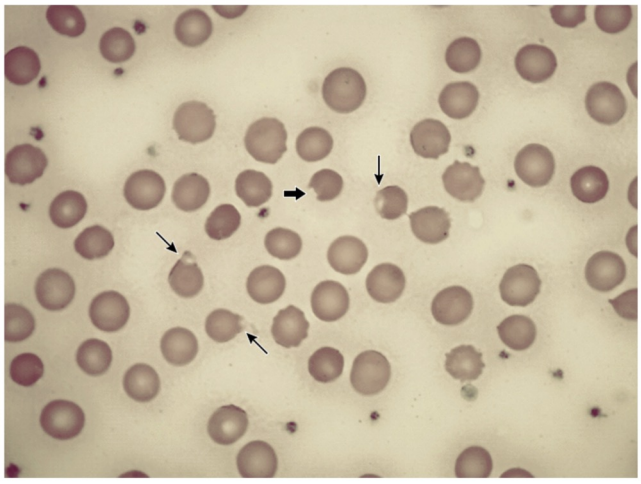
## Bite and Blister Cells:



Examples of a bite cell (thick arrow) and blister cells (arrows) in a patient with G6PD deficiency.

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## Pyruvate Kinase :

- Congenital
- Non spherocytic hemolytic anemia
- Provide protection from malaria
- Northern European
- Heterozygotes

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## Membrane Defect:

- Smear - spherocyte, stomatocyte, elliptocyte

## Hereditary spherocytosis:

- Northern Europe
- Anemia, jaundice, splenomegaly
- Dx. membrane fragility
- Osmotic fragility - detect hemolysis

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## Treatment:

Extrinsic Causes

- Immune mediated, IVIG, steroid, immune suppression,
  Avoid transfusion unless necessary
- TTP - Plasmapheresis
- G6PD - avoid offending agent
- Folic acid
- Splenectomy, BM trans for life threatening hemolysis
- Membrane defect - benefit from splenectomy

Intrinsic Causes

- Folic Acid
- Transfusion
- Iron overload - ineffective hematopoiesis, increased hem
  Metabolism, pigmented gallstone

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## Thalassemia:

- Ratio of alpha to beta globin disrupted
- Destruction of RBC precursors in BM results in ineffective hematopoiesis and causes hemolysis in circulation

## Alpha thalassemia

- One gene deletion, NL CBC, asymptomatic, mild
- Microcytosis
- Two gene deletion (trait) Hb 10-11, decreased Hb A2, MCV 70
- Three gene deletion, Hb H, Hb 7-11, severe microcytosis, Hyperchromic
- Four gene deletion, Hb Barts, Hydrops Fetalis, severe anemia, IU death, stillbirth at 25-40 weeks

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## Beta Thalassemia minor (trait):

- Heterozygous
- Asymptomatic
- MCV 70
- Very mild anemia
- Increase RBC count
- NL RDW
- Hb A2  4-8 percent
- Electrophoresis
- Target cell, tear drop cell

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## Beta Thalassemia Major :

- Def. of beta globin chain causes relative excess of alpha chain
- Ineffective hematopoiesis
- Hemolysis of red cell precursors in the BM
- Destruction of produced RBCs - anemia
- Splenomegaly worsened from sequestration
- Marrow expansion - skeletal deformity, frontal bossing, thin bone cortex, fractures
- Iron overload - transfusion, hyperabsorption in the gut
- Severe anemia, target cell, schistocytes, NRBC
- Increase Hb F, decrease Hb A
- Transfusion dependent

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# Sickle Cell Disease :

- 1-12 African Americans carry the sickle cell trait
- 1-500 African Americans at birth carry - SSD
- 1 in 1000-5000 Hispanic Americans
- Common in the Middle East and Mediterranean
- 3 genotype SS, SC, SB Thal.

# Clinical Features

- Hematologic: Anemia, leukocytosis, thrombocytosis
  - Thrombotic risk, > PE than DVT
- Sickle Cell Crisis: Painful crisis (VOD)
  - Aplastic crisis (parvovirus)
  - Hyperhemolytic crisis
  - Splenic sequestration crisis (Anemia, splenomegaly, hypovolemia, shock)

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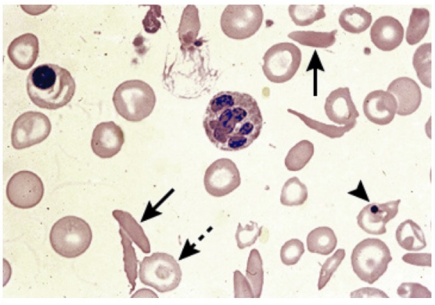
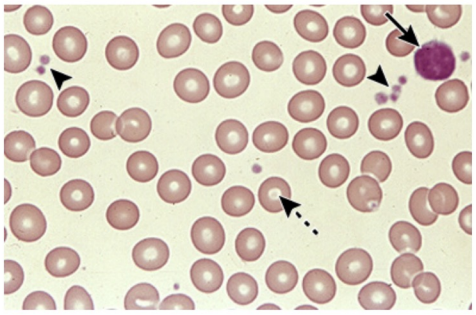
# Peripheral Blood Smear in Sickle Cell:

**Peripheral blood smear in sickle cell anemia**



Peripheral blood smear from a patient with sickle cell anemia. This smear shows multiple sickle cells (arrows). There are also findings consistent with functional asplenia, including a nucleated red blood cell (upper left), a red blood cell containing a Howell-Jolly body (arrowhead), and target cells (dashed arrow).

**Normal peripheral blood smear**



High-power view of a normal peripheral blood smear. Several platelets (arrowheads) and a normal lymphocyte (arrow) can also be seen. The red cells are of relatively uniform size and shape. The diameter of the normal red cell should approximate that of the nucleus of the small lymphocyte; central pallor (dashed arrow) should equal one-third of its diameter.

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## Organ System Involvement :

- Growth
- Bone - infarction, salmonella, osteomyelitis
- GU - Medullary necrosis, priapism
- Cardiac - high output pulmonary hypertension
- Eye - Retinal vessel occlusion
- CNS
- Leg Ulcers
- Infection - encapsulated organism

## Treatment

- Transfusion
- Hydroxyurea  Improve outcome, help prevent stroke, improve O.S.
- Folic Acid
- Pneumovax, meningococcal vaccine
- Annual eye exam
- Iron overload
- Pain

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## Blood Transfusion:

- Indication: reduced oxygen carrying capacity and/or decreased oxygen delivery
- Hemoglobin < 7-8 g/dl, unless acute coronary syndrome
- Acute hemorrhage
- Sickle Cell Anemia
- Chronic transfusion - dependent anemia
- Severe thrombocytopenia at risk of bleeding

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# Thanks


Do you have any questions?
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