<table>
<thead>
<tr>
<th>Anemia</th>
<th>Classification</th>
<th>Etiology</th>
<th>Pathophysiology and Presentation</th>
<th>Lab Findings and Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HYPOPROLIFERATIVE ANEMIAS</strong></td>
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<tr>
<td><strong>IRON DEFICIENCY ANEMIA</strong></td>
<td>Normocytic anemia progressing to hypochromic microcytosis</td>
<td>Adult men and Post-menopausal women: GI blood loss</td>
<td>Decreased exercise capacity</td>
<td>SERUM</td>
<td>Oral iron therapy</td>
</tr>
<tr>
<td></td>
<td>THE MOST COMMON ANEMIA WORLDWIDE</td>
<td>Gastric and duodenal ulcers, IBD, gastric or colonic carcinoma, hemorrhoids, aspirin.</td>
<td>Cheilosis: seen in severe deficiency</td>
<td>Decreased serum iron</td>
<td>Parenteral iron</td>
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<td></td>
<td></td>
<td>Infants and peds: normal negative iron balance during development</td>
<td>Koilonychia</td>
<td>Increased TIBC</td>
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<td></td>
<td></td>
<td>Other diseases: celiac (sprue), gastric bypass, duodenal resection, GI parasites, secondary to intravascular hemolysis</td>
<td>Delayed sensory, motor, and linguistic development in peds</td>
<td>Decreased transferrin saturation</td>
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<td></td>
<td>Pica (e.g. pagophagia)</td>
<td>Decreased serum ferritin</td>
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<td></td>
<td>PERIPHERAL SMEAR</td>
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<td></td>
<td></td>
<td></td>
<td>NO RETICULOCYTOSIS</td>
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<td></td>
<td>Microcytosis (MCV &gt; 80 fL)</td>
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<td>Hypochromism</td>
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<td>MARROW ASPIRATE and Bx</td>
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<td>NML or increased G:E</td>
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<tr>
<td><strong>THE ANEMIA OF INFLAMMATION</strong></td>
<td>Normocytic anemia progressing to hypochromic microcytosis</td>
<td>Underlying Inflammatory Disease</td>
<td>Bacterial polysaccharides or IL-6 → increased hepatic hepcidin expression → inhibition of ferroportin → sequestration of iron in macrophages + enterocytes → increased storage iron and decreased transfer pool</td>
<td>SERUM</td>
<td>Tx underlying disease</td>
</tr>
<tr>
<td><strong>ANEMIA OF CHRONIC DISEASE</strong></td>
<td>THE MOST COMMON ANEMIA in HOSPITALIZED PATIENTS</td>
<td>Pneumonia, malignancy, autoimmune</td>
<td></td>
<td>Decreased serum iron</td>
<td>EPO therapy DOES NOT RESPOND TO EXOGENOUS IRON</td>
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<td>Increased TIBC</td>
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<td>Decreased transferrin saturation</td>
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<td>Decreased serum ferritin</td>
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<td>PERIPHERAL SMEAR</td>
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<td></td>
<td>Identical to iron-deficiency anemia</td>
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<tr>
<td><strong>LOW EPO ANEMIA</strong></td>
<td>Normocytic normochromic</td>
<td>Chronic Kidney Disease (CKD)</td>
<td>Predisposition towards infection</td>
<td>PERIPHERAL SMEAR</td>
<td>IM recombinant EPO</td>
</tr>
<tr>
<td><strong>ANEMIA OF CKD</strong></td>
<td>Endocrine: Hypothyroidism, Hypopituitarism</td>
<td>Endocrine:</td>
<td>Ecchymosis</td>
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<td></td>
<td>Malnutrition</td>
<td>Malnutrition</td>
<td>Epistaxis</td>
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<td></td>
<td>Right Bohr Shift</td>
<td>Right Bohr Shift</td>
<td>Anemic symptoms (fatigue, pallor)</td>
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</table>
### APLASTIC ANEMIA

**Pancytopenic marrow failure**

**Hereditary**
- Fanconi Anemia
- **Idiopathic**: currently thought to be autoimmune, involving cell-mediated attack on marrow precursors
- **Secondary**: radiation, benzene, DDT, myelosuppressive chemotherapy, EBV, Parvovirus B19

**SEROUM**
- INCREASED serum iron due to aplasia of marrow stem cells

**PERIPHERAL SMEAR**
- NO RETICULOCYTOSIS
- Microcytosis (MCV > 80 fL)
- Hypochromism

**MARROW ASPIRATE and Bx**
- NML or increased G:E

**ABx**
- Transfuse RBCs Platelets
- ISD (cyclosporine, GCs, ATG)
- Allogenic bone marrow transplant

### HEMORRHAGIC ANEMIAS

**BLOOD LOSS ANEMIA**

**Normocytic normochromic Hemodilution effect**

**Hemorrhage**
- The decreased Hct is due to hemodilution (due to transfusion with colloid or EXCF and ICF volume shifts)

**ACUTE**: no change in RBC count due to lack of ECV expansion
**CHRONIC (> 7 d)**: Increased erythropoesis and marrow expansion

**PERIPHERAL SMEAR**
- NO RETICULOCYTOSIS until > 7 d. after blood loss anemia

**MARROW ASPIRATE and Bx**
- Decreased G:E due to erythropoesis

**ABx**
- Transfuse while blood or packed cells

### MACROCYTIC ANEMIAS

**PERNICIOUS ANEMIA**

**Megaloblastic macrocytic**

**Ineffective erythropoesis**

**Autoimmune atrophic gastritis**
- Mediated by autoAbs to gastric parietal cells, and to IF
- Results in lack of absorption of B12

**Hereditary**
- AR inheritance. LOF mutation in IF.

**Associated with**: myxedema (hyperthyroidism), DM, gastritis
- Achlohydria, achylia, rugal atrophy
- Glossitis + atrophic papillae (smooth erythematous appearance)

**Neurologic deficits**: diminished vibratory sense (dorsal columns), loss of proprioception (dorsal columns and DCST), spastic paralysis (LCST), Parasthesia

**Anti-parietal Abs**: high sensitivity and low specificity
**Anti-IF Abs**: low sensitivity and high specificity
- Serum LDH and bilirubin are increased
- Peripheral smear shows canonical signs
- **Direct serum B12 levels (low specificity)**
- Should be considered in all cases

**ABx**
- If treated with folate solely: leads to progression of neurological decline
- IM B12
- Folate supplement
| B12 DEFICIENCY | Meataloblastic macrocytic with nutritional cause | Incoordinated nocturnal ambulation (due to loss of proprioception)  
Megaloblastic Madness: incontinence, dementia, spasticity of lower extremities | patients with unexplained dementia or neuropathy  
Schilling Test: can be used to measure absorption of B12 by quantifying urinary excretion of free radiolabled substrate |

| | Megaloblastic macracytic with nutritional cause | B12 is involved in two critical reactions  
**Conversion of methylmalonyl-CoA to succinyl-coA**  
Deficient mutase activity is the main cause of neurologic disease  
**Conversion of homocysteine to methionine**  
Met deficiency results in demylination of the DCS and LCST but neurologic disease is not seen in folate deficiency | SERUM  
Increased MMA  
Increased homocysteine  
Increased LDH  
Increased direct bilirubin due to medulalry hemolysis  
PERIPHERAL SMEAR  
CBC: pancytopenia is severe deficiency  
Non-elevated reticulocyte count (ineffective erythropoiesis)  
Hypersegmented neutrophils  
Macrocrtes  
Circulating megaloblasts  
MARROW ASPIRATE and Bx  
Demonstrates evidence of ineffective erythropoiesis due to apoptotic destruction of erythroid in the marrow  
Megaloblasterosis: immaturity of nuclei in erythroid and myeloid precursors  
Hypercellularity in the erythroid and myeloid lines  
**Giant band cells**  
Macrocytosis and N:C dissociation in most mitotic |
HEMOLYTIC ANEMIAS

<table>
<thead>
<tr>
<th>General Features of Hemolysis</th>
<th>FOLATE DEFICIENCY</th>
<th>labile cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia results with the RBC lifespan &lt; 20 d.</td>
<td>Dietary: lack of vegetables and dairy</td>
<td>All findings are identical to B12 deficiency</td>
</tr>
<tr>
<td>Aplastic crisis may occur with chronic hemolytic anemia and infection with Parvovirus B19</td>
<td>Malabsorption: celiac disease, deconjugase deficiency</td>
<td>BUT</td>
</tr>
<tr>
<td>Results in a flu-like illness with transient erythrocyte aplasia</td>
<td>Pregnancy</td>
<td>MMA is not elevated</td>
</tr>
<tr>
<td>Results in folate deficiency due to increased erythropoiesis</td>
<td>Hemolytic Anemia</td>
<td></td>
</tr>
<tr>
<td>Expanded medullary space may result in skeletal deformities (hereditary hemolytic anemias)</td>
<td>Alcoholism: decreased intake, decreased absorption, cirrhosis and decreased storage</td>
<td></td>
</tr>
<tr>
<td>Severe hereditary hemolysis results in extramedullary hematopoeisis and tumor-like lesions on the axial skeleton.</td>
<td>Phenytin</td>
<td></td>
</tr>
<tr>
<td>Kernicterus: hemolytic anemia in neonates results in deposition of direct bilirubin in the basal ganglia.</td>
<td>Medications: methotrexate, TMP-sulfa</td>
<td></td>
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<tr>
<td>Gallstones: seen in chronic hemolysis</td>
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<tr>
<td>Hemosiderosis is rare in chronic hemolysis</td>
<td>Iron overload: results from increased absorption (decreased hepcidin) and repeated transfusion</td>
<td></td>
</tr>
<tr>
<td>Disseminated Intravascular Coagulation (DIC): seen in acute intravascular hemolysis due to liberation of RBC phospholipids</td>
<td>Severe hemolysis results in extramedullary hematopoeisis and tumor-like lesions on the axial skeleton.</td>
<td></td>
</tr>
<tr>
<td>In ABO reactions, complement activation results in shock</td>
<td>Kernicterus: hemolytic anemia in neonates results in deposition of direct bilirubin in the basal ganglia.</td>
<td></td>
</tr>
<tr>
<td>HEREDITARY SPHEROCYTOSIS (HS)</td>
<td>Extravascular Hemolysis</td>
<td>SERUM</td>
</tr>
<tr>
<td>AD inheritance</td>
<td>Mutations within the ankyrin gene (chromosome 8) → deficit in spectrin → progressive membrane loss</td>
<td>Increased indirect bilirubin</td>
</tr>
<tr>
<td>Extravascular Hemolysis</td>
<td>In newborns: kernicterus</td>
<td>Increased LDH</td>
</tr>
<tr>
<td>Throughout NH: bilirubin gallstones</td>
<td>Cholecystitis is an early indicator of HS</td>
<td></td>
</tr>
<tr>
<td>Splenectomy if &gt; 5 yrs</td>
<td>Pneumococcal vaccine</td>
<td></td>
</tr>
</tbody>
</table>

PERIPHERAL SMEAR
Spherocytes > 20%: round cells
| TRAUMATIC HEMOLYTIC ANEMIA | Intravascular Hemolysis | Microvascular endothelial damage: vasculitis, malignant HTN  
Cardiac: valve prostheses (aortic, mitral) with fibrin deposition, aortic valve dissection  
Microangiopathic Hemolytic Anemia: deposition of fibrin and platelet plugs in small vessels  
TTP: microthrombi result in renal failure, neurological deficits, fever, thrombocytopenia, and MHA  
HUS: in peds, occurign after viral URIs and EHEC  
DIC, disseminated carcinoma, pre-eclampsia | Cardiac valve hemolysis is typically asymptomatic and compensated  
SERUM  
Increased indirect bilirubin  
Increased LDH  
Decreased TIBS and saturation (iron depletion)  
PERIPHERAL SMEAR  
Schistocytes: diagnostic of traumatic hemolysis. These are RBC fragments.  
MARROW ASPIRATE and Bx  
Hypercellularity  
URINE  
Hemosiderinuria  
Hemoglobinuria  
Methemoglobinuria |
|---|---|---|---|
| PYRUVATE KINASE DEFICIENCY | AR inheritance  
Extravascular Hemolysis  
MOST COMMON GLYCOLYTIC DEFECT  
Affects Northern Europeans | PK deficiency → increased intracellular 2,3 DPG due to flux through the Rapaport-Luebering pathway → increased peripheral O2 delivery → anemic tolerance  
Chronic hemolytic anemia  
Infancy and peds: anemia and jaundice |  
| G6PD DEFICIENCY | X-linked inheritance | Deficient G6PD → depletion of NADPH → depletion of GSH pools and catalase → oxidation of HgB  
GDPD B: normal WT variant  
GDPD A: variant with normal function. Used to verify that tumor | Direct assay of RBC G6PD activity |
**Mixed intravascular and extravascular hemolysis**

**MOST COMMON RBC METABOLIC DEFECT**

Affects Africans, Med basin, Middle East

and membrane SH → formation of disulfide bridges between globin and RBC membrane → Heinz bodies → non-deformability → extravascular hemolysis

With severe oxidative stress: oxidation of membrane SH results in perforation and intravascular hemolysis

Drugs may trigger hemolysis in the oxidative variants of G6PD deficiency:
- Sulfamethoxizole
- Nitrofurantoin
- Primaquine
- Dapsone

**ANEMIAS OF DISORDERD GLOBIN SYNTHESIS**

| SICKLE CELL DISEASE (SCD) | Chronic Extravascular Hemolysis | Glu6 → Val substitution in the β subunit of HbA. Results in polymerization of the deoxegenated form of HbS. Repeated sickling and expansion results in permanent cellular deformity. | Hemolytic Anemia | Vaso-occlusive crises | Sickled cells are prone to conglomeration in the small vessels. Hemolysis liberates heme, depleting NO and arginine (via release of arginase). Vasoconstriction Platelet aggregation Endothelial activation Recurrent painful crises (typically dactylitis) Requires hospitalization and transfusion if vasoocclusive | Acute Chest Syndrome: tachypnea, hypoxia, pain, fever, cough, infiltrates. | **PERIPHERAL SMEAR** | Sickled Cells HJ Inclusions Targetoid cells Anisoscytosis, Poikilocytosis Reticulocytosis **ELECTROPHORESIS** HbSS, HbS + HbA2, HbSC Charge variation allows for good separation of various Hb. | **MANAGEMENT OF PAINFUL CRISIS** | Allogenic bone marrow |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | |
| | | | | | | | | | |

**Sickle Trait:** HbAS

Typically asymptomatic Polyuria due to medulalry gradient collapse Painless hematuria Sickling with severe dehydration or altitidue

**PERIPHERAL SMEAR**

Sickled Cells HJ Inclusions Targetoid cells Anisoscytosis, Poikilocytosis Reticulocytosis **ELECTROPHORESIS** HbSS, HbS + HbA2, HbSC Charge variation allows for good separation of various Hb. **MANAGEMENT OF PAINFUL CRISIS**

Analgesics (narcotics), hydration, NSAIDs, supplemental O2, exchange transfusion

Prophylactic PCN Pneumovax Hydroxyurea (increases HbF) Iron chelation
<table>
<thead>
<tr>
<th>αThalassemia Syndromes</th>
<th>Hypochromic microcytic erythropoiesis</th>
<th>Chronic extravascular hemolysis</th>
<th>Typically involve deletion of α globin alleles (chromosome 16).</th>
</tr>
</thead>
<tbody>
<tr>
<td>αThalassemia carrier</td>
<td>αα/α-</td>
<td></td>
<td>α-thalassemia trait</td>
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<tr>
<td></td>
<td>Asymptomatic without anemia</td>
<td>Elevated Bart’s hemoglobin (γ₄)</td>
<td></td>
</tr>
<tr>
<td>α-thalassemia trait</td>
<td>α/-α-: prevalent in Med and Africa</td>
<td>Increased incidence of thalassemia trait and silent carriers</td>
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<tr>
<td></td>
<td>α/-α- and αα/--: prevalent in East Asia</td>
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<tr>
<td></td>
<td>Hypochromic microcytosis</td>
<td>Hypoxic microcytosis</td>
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<td></td>
<td>Negligible anemia</td>
<td>HbH disease</td>
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<td>α/α-</td>
<td></td>
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<td></td>
<td>Chronic extravascular hemolytic anemia due to HbH (β₄) inclusions</td>
<td>HbH disease</td>
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<td>Transfusion if necessary</td>
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<td>Folci acid supplement</td>
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<td>Splenectomy</td>
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</tbody>
</table>

Renal papillary necrosis

\[ β^5β^0 \] results in severe anemia

Heterozygosity with α thalassemia trait decreases HbS concentrations

HbSβ⁰ results in severe anemia

SERUM

Increased indirect bilirubin

Increased LDH

Resembles ARDS.

Associated with local or remote infection.

**Stroke:** subclinical infarction

**Chronic ischemic damage:** Aseptic osteonecrosis of the femoral head, Pulmonary HTN

CKD, Retinopathy

**Functional Asplenia**

Predisposition to infection and sepsis

Splenectomy leads to stabilization of acute anemia (decreased sequestration)

The disease typically becomes symptomatic > 6 mo. due to conversion to β chain synthesis.

**α thalassemia syndromes**

All hemoglobins are affected

May detect Bart’s hemoglobin

Transfusion if necessary

Folci acid supplement

Splenectomy
| **β THALASSEMIA SYNDROMES** | Hypochromic microcytic inactivity | Chronic extravascular hemolysis | Various mutations within the β globin coding region of chromosome 11 → decreased synthesis (Typically not a deletion) | **β thalassemia minor** (Hb > 9 d/dL)  
Typically β/β+  
Asymptomatic with negligible anemia  
DESPITE microcytosis (r/o iron deficiency and inflammation) | **β thalassemia intermedia** (Hg 6-9 g/dL)  
Typically β+/β+, β+/β0, β/β0  
Microcytic anemia with several aberrant RBC morphologies (targetoid, nucleated blasts) | **β thalassemia major** (Hb < 6 g/dL)  
β0/β0  
α4 hemoglobin precipitates, resulting in  
Ineffective erythropoiesis  
Extravascular hemolysis  
Severe microcytic anemia  
Hepatosplenomegaly  
Marrow expansion and bone deformity  
Increased GI iron absorption and transfusion hemochromatosis | Screen maternal MCV and ferritin  
**Suspect thalassemia with microcytosis and NML ferritin**  
**β thalassemia intermedia**  
Transfusion if necessary  
Folci acid supplement  
Splenectomy  
**β thalassemia major**  
Transfusion  
Iron chelation  
Allogenic stem cell transplant  
Splenectomy |

Hypochromic microcytosis  
Hemolysis is typically compensated  
Targetoid cells  
Oxidant drugs provoke hemolysis  

**Hydrops Fetalis**  
--/--  
Most Hb is Bart’s (high O2 affinity and low delivery)  
Mortality is due to hepatic failure (ischemia and extramedullary hemato poiesis)